



**Department of Community Genetics
Public Health Services
Ministry of Health
Israel**

**MENDELIAN DISORDERS IN
THE NON JEWISH
POPULATION OF ISRAEL**

Joël Zlotogora M.D., Ph.D.

January 2015

The catalogue includes Mendelian diseases that have been reported in the literature and were diagnosed in the Arab and Druze population of Israel or were reported as Palestinian Arabs and are either relatively frequent or were first reported in this population.

The catalogue is not complete and it does not include all the diseases that have been diagnosed in this population. It is planned that with the help of the physicians involved the next editions will be more complete.

The catalogue includes a very short list of references and mainly refers to McKusick's Mendelian Inheritance in Man: <http://www.ncbi.nlm.nih.gov/Omim>.

Please contact me if there is any inaccurate or forgotten data.

The online updated catalog is available at <http://server.goldenhelix.org//israeli/>

The data is also available at www.health.gov.il/genetics

Joël Zlotogora M.D., Ph.D.
e-mail zlotogora@gmail.com

Aarskog syndrome (Faciogenital dysplasia)

X linked recessive (MIM 305400)

The disorder is characterized by embryonic ocular hypertelorism, anteverted nostrils, broad upper lip, and shawl scrotum. Affected males can reproduce. The ligamentous laxity manifest by hyperextensibility of the fingers, genu recurvatum, and flat feet. Furthermore, hypermobility in the cervical spine with anomaly of the odontoid resulted in neurologic deficit. The affected individuals demonstrate clinical variability particularly in their cognitive skills. The incidence of mental handicap in Aarskog syndrome is less than 30% of affected males.

Epidemiology:

The disease was diagnosed in one large Muslim Arab family.

Molecular genetics:

FDG1 *gene* (*chromosomal locus Xp11.21*).

The patients carries a 2189delA mutation in exon 15.

References:

Shalev SA, Chervinski E, Weiner E, Mazor G, Friez MJ, Schwartz CE. Clinical variation of Aarskog syndrome in a large family with 2189delA in the FGD1 gene. *Am J Med Genet A*. 2006;5;140:162-165.

Abetalipoproteinemia

Autosomal recessive (MIM 200100)

The first symptoms are early failure to thrive with diarrhea and steatorrhea, often with abdominal distention. While with time the steatorrhea is less marked, other symptoms appear, including neurological, ophthalmological, and hematological manifestations. The neurological manifestations of the disorder are of a spinocerebellar degenerative syndrome. The first symptoms are usually unsteadiness in walking and diminution of the deep tendon reflexes up to areflexia. Vibratory senses and proprioception are progressively lost and ataxia appears; untreated patients are unable to stand alone by the third decade of life. In addition, muscle weakness is frequently observed. The intellectual development is normal in the affected individuals. Ocular symptoms are those of atypical retinitis pigmentosa with decreased visual acuity, night blindness and pigmentary changes of the retina. The hematological manifestations may include severe anemia; the most characteristic finding is an abnormal form of the erythrocytes: acanthocytes, which represent some 50% of all red blood cells.

The gastrointestinal symptoms respond to restriction of triglycerides containing long chain fatty acids. The supplementation of the diet with tocopherol (vitamin E) appears to inhibit the progression of the neurological symptoms as well as the retinopathy.

The diagnosis is based on the clinical features and the findings of acanthocytes in the blood smear. It is confirmed by the lipid profile which is characteristic for the disease.

Epidemiology and molecular genetics

Microsomal triglyceride-transfer protein (MTP), gene (chromosomal locus 4q22-24)

A large genomic deletion in homozygosity was found in one Muslim Arab patient.

References

Benayoun L, Granot E, Rizel L, Allon-Shalev S, Behar DM Ben-Yosef T.
Abetalipoproteinemia in Israel: Evidence for a founder mutation in the Ashkenazi Jewish population and a contiguous gene deletion in an Arab patient. *Molecular Genetics and Metabolism* 2007;90;453-457

Achromatopsia, total color blindness

Autosomal recessive (MIM 216900)

Total color blindness is sometimes referred to as 'absence of cones'; in fact cones are present but functionally defective. Since the cones are defective the subjects affected with total color blindness see better at night. As infants, the patients have nystagmus, which decreases later. Photophobia is striking. Patients squint even in light of ordinary intensity. Vision in ordinary lighting is severely restricted; vision in dim light is relatively better. Colors cannot be distinguished. Fundoscopic examination is normal.

Epidemiology:

The disease was diagnosed in several Arab families in Israel.

Molecular genetics:

Cone photoreceptor cGMP-gated cation channel CNGA3 gene (chromosomal locus 2).
The founder mutation c.1585G>A, V529M was found in Arab muslim families. Other mutations were found in single families c.1207C>T (p.R403X), p.G329C and G333C

References:

Arbour NC, Zlotogora J, Knowlton RG, Merin S, Rosenmann A, Kanis AB, Rokhlina T, Stone EM, Sheffield VC: Homozygosity mapping of achromatopsia to chromosome 2 using DNA pooling. *Hum Mol Genet* 1997; 6: 689-694.
Zelinger L, Greenberg A, Kohl S, Banin E, Sharon D. An ancient autosomal haplotype bearing a rare achromatopsia-causing founder mutation is shared among Arab Muslims and Oriental Jews. *Hum Genet.* 2010;128:261-267.

Acrodermatitis enteropathica

Autosomal recessive (MIM 201100)

The disorder is characterized by intermittent simultaneous occurrence of diarrhea and dermatitis with failure to thrive. Alopecia of the scalp, eyebrows, and eyelashes is a usual feature. The skin lesions are bullous.

Acrodermatitis enteropathica is distinct from zinc deficiency of neonates fed on breast milk in several ways. Zinc deficiency in breastfed babies is caused by low levels of zinc in the maternal milk, whereas in acrodermatitis enteropathica, the maternal milk is protective and the symptoms of zinc deficiency develop after weaning.

Serum alkaline phosphatase is low in patients with acrodermatitis enteropathica and that it returns to normal with zinc therapy. Alkaline phosphatase is a zinc metalloenzyme.

Epidemiology:

The disease was diagnosed in two Muslim Arab families from a village in Israel.

Molecular genetics:

Intestinal zinc transporter SLC39A4 gene (chromosomal locus 8q24.3).

The patients were homozygotes for c1223delC; p.A408fsX481

References:

Vardi A, Anikster Y, Eisenkraft A, Shohat M, Abu-Much J, Eisenkraft S, Sredni B, Nir U. A new genetic isolate of acrodermatitis enteropathica with a novel mutation. *Br J Dermatol.* 2009;160:1346-1348.

Acute infantile liver failure due to mutations in TRMU gene

Autosomal recessive (MIM 610230)

Acute liver failure in infancy is a life threatening condition manifested by poor feeding, vomiting jaundice, hemorrhagic diathesis irribilability and hypoactivity. A group of patients presenting at the age of 2-4 months requiring intensive care because of acute liver failure survived and the liver functions returned to normal. The survivors never had a recurrence, the longest follow-up period was 14 years.

Molecular genetics:

TRMU gene (chromosomal locus 22q13)

A muslim Arab patient was compound heterozygous for V279M/c.500-510del

References

Zeharia A, Shaag A, Pappo O, Mager-Heckel AM, Saada A, Beinat M, Karicheva O, Mandel H, Ofek N, Segel R, Marom D, Rötig A, Tarassov I, Elpeleg O. Acute Infantile Liver Failure Due to Mutations in the TRMU Gene. *Am J Hum Genet.* 2009; 85:401-4077.

Adrenal hyperplasia III (classical 21 OH deficiency)

Autosomal recessive (MIM 201910)

There are 4 recognized clinical forms of congenital adrenal hyperplasia, the majority of cases being associated with 21-hydroxylase deficiency: salt-wasting (SW), simple virilizing (SV), non-classical (NC) late-onset (also called attenuated and acquired), and cryptic. All 4 forms are closely linked to HLA and represent the effects of various combinations of alleles.

Epidemiology:

21-hydroxylase deficiency seems to be relatively frequent among Arabs in Israel. No data on the incidence are available.

Molecular genetics:

CYP21B gene (chromosomal locus 6p21.3).

Among the patients in Israel the most frequent mutation is [I2 splice]. Other frequent mutations are: [Q318X], [I172N], [8bp deletion] and [V281L] (Israeli S)

Afibrinogenemia congenital

Autosomal recessive (MIM 202400)

The blood is completely incoagulable, yet some of the affected persons have remarkably little trouble with bleeding. In some cases the disorder was detected at birth because of excess bleeding from the umbilical stump.

In the Palestinian family two sisters were affected and presented with serious intracranial bleeding after non significant trauma.

Epidemiology

The disorder was described in one Palestinian family

Molecular genetics

Fibrinogen beta polypeptide FGB gene (chromosomal locus 4q28)

The patients were homozygous for [W467X]

References

Neerman-Arbez M, Vu D, Abu-Libdeh B, Bouchardy I, Morris MA. Prenatal diagnosis for congenital afibrinogenemia caused by a novel nonsense mutation in the FGB gene in a Palestinian family. *Blood* 2003;101:3492-3494.

Aicardi Goutieres syndrome

Autosomal recessive (MIM 225750)

Aicardi-Goutieres syndrome is phenotypically similar to in utero viral infection. It is a genetically heterogeneous autosomal recessive encephalopathy characterized by cerebral atrophy, leukodystrophy, intracranial calcifications, chronic cerebrospinal fluid lymphocytosis, increased CSF alpha-interferon and negative serologic investigations for common prenatal infections. Severe neurologic dysfunction becomes clinically apparent in infancy, and manifests as progressive microcephaly, spasticity, dystonic posturing, profound psychomotor retardation, and often death in early childhood. Outside the nervous system, thrombocytopenia, hepatosplenomegaly, and elevated hepatic transaminases along with intermittent fever may also erroneously suggest an infective process Encephalopathy which closely mimic the sequelae of congenital infection.

Epidemiology

The disorder was described in one Muslim Arab family

Molecular genetics

Heterogeneous

SAMHD1 gene (chromosomal locus 20q11)

The patients were homozygous for [p.120_123 del]

References

Rice GI, Bond J, Asipu A, Brunette RL, Manfield IW, Carr IM, Fuller JC, Jackson RM, Lamb T, Briggs TA, Ali M, Gornall H, Couthard LR, Aeby A, Attard-Montalto SP, Bertini E, Bodemer C, Brockmann K, Brueton LA, Corry PC, Desguerre I, Fazzi E, Cazorla AG, Gener B, Hamel BC, Heiberg A, Hunter M, van der Knaap MS, Kumar R, Lagae L, Landrieu PG, Lourenco CM, Marom D, McDermott MF, van der Merwe W, Orcesi S, Prendiville JS, Rasmussen M, Shalev SA, Soler DM, Shinawi M, Spiegel R, Tan TY, Vanderver A, Wakeling EL, Wassmer E, Whittaker E, Lebon P, Stetson DB, Bonthron DT, Crow YJ. Mutations involved in Aicardi-Goutières syndrome implicate SAMHD1 as regulator of the innate immune response. *Nat Genet.* 2009;41:829-832.

Albinism, oculocutaneous

Autosomal recessive (MIM 203100)

Oculocutaneous albinism type I (OCA1) is an autosomal recessive disorder characterized by absence of pigment in hair, skin, and eyes, nystagmus, photophobia, and reduced visual acuity. There is a decussation defect in the optic tracts; an abnormal proportion of fibers from the ganglion cells of the temporal retina decussate to the contralateral cerebral hemisphere. This accounts, at least in part, for the uncorrectable defective central fixation and ocular nystagmus. Homozygotes lack tyrosinase, which catalyzes the first 2 steps, and at least 1 subsequent step, in the conversion of tyrosine to melanin.

Epidemiology:

Oculocutaneous albinism seems to be relatively frequent among Arabs in Israel and was diagnosed in several villages.

Molecular genetics:

Tyrosinase gene, TYR (chromosomal locus 11q14-q21).

Several mutations were characterized, among them IVS2-1G, c.757G>A (p.G253R), p.R299C, c.896G>A (p.R299H) p.R402X p.S50X among Christians and IVS1-7116-IVS2+7677 in a Muslim family

References:

Rosenmann A, Bejarano-Achache I, Eli D, Maftsir G, Mizrahi-Meissonnier L, Blumenfeld A. Prenatal molecular diagnosis of oculocutaneous albinism (OCA) in a large cohort of Israeli families. *Prenat Diagn* 2009;29:939-946.

Allgrove syndrome (Achalasia-addisonianism- alachrimia syndrome, AAA,)

Autosomal recessive (MIM 231550)

The syndrome includes glucocorticoid deficiency and achalasia of the stomach cardia. The patients have also defective tear formation (alacrima) and may show other signs of autonomic dysfunction. There may be other features such as the significant impairment of the central nervous system, delay in motor and speech developments, ataxia, and others.

Epidemiology and molecular genetics

Aladin AAAS gene (chromosomal locus 12q13).

The disease was diagnosed in **one Muslim Arab family** (Shalev S) in which the patients were homozygotes for [Q15K] and in a Palestinian family. in which the patients were homozygous for [IVS5+1G>A]

References:

Ismail EA, Tulliot-Pelet A, Mohsen AM, Al-Saleh Q. Allgrove syndrome with features of familial dysautonomia: a novel mutation in the AAAS gene. *Acta Paediatr.* 2006;5:1140-1143.

Alkaptonuria

Autosomal recessive (MIM 203500)

The disorder is due to the failure to metabolize homogentisic acid, which is excreted in the urine, and darken at air. The patients may present with ochronosis and or osteoarthritis.

Epidemiology:

Several individuals affected with alkaptonuria were diagnosed in an extended **Bedouin tribe from the Negev**.

Molecular genetics:

Homogentisate 1,2 deoxygenase gene (chromosomal locus 3q21-q23).

The mutation c.16-272_87+305del was diagnosed in one family (Morad Khayat)

References:

Hendel H, Ben Assa BJ. Alkaptonuria in a Beduin kinship. In: Goldschmith E ed. The genetics of migrant and isolated populations. 1963. William and Wilkin co N.Y. p 301

Alopecia neurological defect and endocrinopathy syndrome

Autosomal recessive (MIM)

In a consanguineous kindred of Arab Moslem were reported with a complex syndrome consisting of alopecia, neurological defects, and endocrinopathy (ANE syndrome). Patients were found to display hair loss of widely varying severity. A skin biopsy obtained from scalp skin revealed absence of mature hair follicles; instead, only rudimentary infundibula and epithelial cysts were observed in the dermis. Neurological impairment consisted of moderate to severe mental retardation and progressive motor deterioration, which started in all affected siblings during their second decade of life. Progressive motor decline was found to result from combined upper and lower motor dysfunction. Extensive endocrinological evaluation revealed central hypogonadotropic hypogonadism manifesting with delayed or absent puberty and central adrenal insufficiency. Brain magnetic resonance imaging (MRI) revealed a hypoplastic pituitary gland with preserved hypothalamus but no evidence for basal ganglia or white-matter disease. Additional features included short stature, microcephaly, gynecomastia (Figure 1E), flexural reticulate hyperpigmentation, hypodontia, kyphoscoliosis, multiple facial pigmented nevi, ulnar deviation of hands, and loss of subcutaneous fat.

Epidemiology:

The disease has been reported in a Muslim Arab family.

Molecular genetics:

RBM28 (chromosomal locus 7q31-q32)

All the patients are homozygous c.T1052C .

References:

Nousbeck J, Spiegel R , Ishida-Yamamoto A, Indelman M , Shani-Adir A , Adir N , Lipkin E , Bercovici S , Geiger D, van Steensel MA, Steijlen PM , Bergman R, Bindereif A , Choder M , Shalev S, Sprecher E Alopecia, Neurological Defects, and Endocrinopathy Syndrome Caused by Decreased Expression of RBM28, a Nucleolar Protein Associated with Ribosome Biogenesis. *Am J Hum Genet* 2008;82:1114-121.

Aplasia cutis congenita, high myopia and cone rod dysfunction

Autosomal recessive (MIM 601075)

A brother and sister with aplasia cutis congenita, high myopia and cone rod dysfunction was described in a Christian Arab family. It was suggested that this represent a new autosomal recessive syndrome.

References:

Gershoni-Baruch R, Leibo R. Aplasia cutis congenita, high myopia and cone rod dysfunction in two sibs: a new autosomal recessive disorder. Am J Med Genet 1996; 61:42-44.

Arrhythmogenic right ventricular dysplasia, familial ARVD 8

Autosomal recessive (MIM 607450)

Arrhythmogenic right ventricular dysplasia (ARVD) is a heterogeneous heart muscle disorder causing arrhythmia and sudden cardiac death. In this autosomal recessive form all the patients have woolly hair, and an exceptionally dry skin in all part of the body beginning at birth. During childhood they present with a pemphigous-like skin disorder including vesiculous lesions on the extremities particularly knees palms and soles.

Epidemiology:

The disease has been diagnosed in several individuals from a Muslim Arab family originating from the **region of Jerusalem**.

Molecular genetics:

desmoplakin gene, DSP (chromosomal locus 6p24).

The Palestinian patients from the region of Jerusalem are homozygote for a novel mutation [G2375A].

References:

Alcalai R, Metzger S, Rosenheck S, Meiner V, Chajek-Shaul T. A recessive mutation in desmoplakin causes arrhythmogenic right ventricular dysplasia, skin disorder, and woolly hair. *J Am Coll Cardiol*. 2003;42:319-327.

Arthrogryposis multiplex congenita

Autosomal recessive (MIM 208100)

Arthrogryposis multiplex congenita is a symptom characterized by non-progressive joint contractures that involve more than one part of the body. This is a heterogeneous group of disorders and may result from different mechanisms that caused decreased movements in utero. There have been several reports of genetic forms of the syndrome.

An autosomal recessive form has been diagnosed in several related Muslim Arab families in **one Muslim Arab village**. This form of the syndrome is present at birth and expressed mainly by flexion contractures at the knees and elbows with muscle hypotrophy/weakness around the involved joints. Neurologic examination and electrophysiological studies demonstrated that it represents a neuropathic type of arthrogryposis. The syndrome was milder in females and it may also be that the penetrance is incomplete among females.

In this large kindred, the gene has been mapped to 5qter.

The disease was reported in two siblings from a Muslim family from East Jerusalem. In the brother of the affected siblings who married a first cousin a more severe form with intrauterine contracture was diagnosed in two fetuses

Molecular genetics:

Nesprin-1 SYNE-1 (chromosomal locus 6q25

In the family from Jerusalem the affected were homozygous for a A>G substitution of the acceptor site at the junction intron 136-137

References:

- Attali R, Warwar N, Israel A, Gurt I, McNally E, Puckelwartz M, Glick B, Nevo Y, Ben-Neriah Z, Melki J. Mutation of SYNE-1, encoding an essential component of the nuclear lamina, is responsible for autosomal recessive arthrogryposis. *Hum Mol Genet.* 2009;18:3462-32469.
- Jaber L, Weitz R, Bu X, Fischel-Ghodsian N, Rotter JI, Shohat M. Arthrogryposis multiplex congenita in an Arab kindred: update. *Am J Med Genet* 1995 55:331-334.
- Shohat M, Lotan R, Magal N, Shohat T, Fischel-Ghodsian N, Rotter J, Jaber L. A gene for arthrogryposis congenita neuropathic type is linked to D5S394 on chromosome 5qter. *Am J Hum Genet* 1997;61:1139-1143.

Arthrogryposis renal dysfunction and cholestasis (ARC) syndrome

Autosomal recessive (MIM 208085)

The patients typically presents with neonatal cholestatic jaundice, renal tubular leak and hypotonia related arthrogryposis. Other variable features includes ichthyosis, mild dysmorphism, absent corpus callosum and recurrent infections. In 25% of the patients present with a platlet storage pool defect similar to grey platlets syndrome.

Epidemiology:

The syndrome has been diagnosed in a Muslim Arab and a Druze family

Molecular genetics:

VPS33B gene (chromosomal locus 15q26.1)

In one Muslim Arab family the mutation was identified c. 403+1G>A, in the Druze family the mutation was D234H

VIPAR gene

In one Muslim Arab family the mutation was identified R270X

References:

- Cullinane AR, Straatman-Iwanowska A, Zaucker A, Wakabayashi Y, Bruce CK, Luo G, Rahman F, Gürakan F, Utine E, Ozkan TB, Denecke J, Vukovic J, Di Rocco M, Mandel H, Cangul H, Matthews RP, Thomas SG, Rappoport JZ, Arias IM, Wolburg H, Knisely AS, Kelly DA, Müller F, Maher ER, Gissen P. Mutations in VIPAR cause an arthrogryposis, renal dysfunction and cholestasis syndrome phenotype with defects in epithelial polarization. *Nat Genet.* 2010;42:303-312. Epub 2010 Feb 28. Erratum in: *Nat Genet.* 2011;43:277.
- Gissen P, Tee L, Johnson CA, Genin E, Caliebe A, Chitayat D, Clericuzio C, Denecke J, Di Rocco M, Fischler B, Fitzpatrick D, Garcia-Cazorla A, Guyot D, Jacquemont S, Koletzko S, Leheup B, Mandel H, Sanseverino MT, Houwen RH, McKiernan PJ, Kelly DA, Maher ER. Clinical and molecular genetic features of ARC syndrome. *Hum Genet.* 2006; 120:396-409.
- Hershkovitz D, Mandel H, Ishida-Yamamoto A, Chefetz I, Hino B, Luder A, Indelman M, Bergman R, Sprecher E. Defective lamellar granule secretion in arthrogryposis, renal dysfunction, and cholestasis syndrome caused by a mutation in VPS33B. *Arch Dermatol.* 2008;144:334-340.

Aspartylglucosaminuria

Autosomal recessive (MIM 208400)

Aspartylglucosaminuria is a slowly progressive disorder. The main clinical findings are coarse facial features, skeletal abnormalities and mental retardation. Because of the progressive nature of the disease early diagnosis is difficult when the patient presents with mild mental retardation in particular since in most cases there is no visceromegaly. With age the facial appearance may become coarser suggesting a storage disease. This is a lysosomal storage disease caused by aspartylglucosaminidase deficiency. A first clue to the biochemical diagnosis is the demonstration that the patients excrete at early stages large amounts of aspartylglucosamine in the urine by chromatography.

Epidemiology:

Aspartylglucosaminuria has been diagnosed in 4 non-related Arab families originating from the **region of Jerusalem**.

Molecular genetics:

Aspartylglucosamine gene, AGA (chromosomal locus 4q32-q33).

All the Palestinian patients from the region of Jerusalem are homozygote for a novel mutation [S72P].

References:

- Peltola M, Tikkanen R, Peltonen L, Jalanko A. Ser72Pro active-site disease mutation in human lysosomal aspartylglucosaminidase: abnormal intracellular processing and evidence for extracellular activation Hum Mol Genet 1996;5:737-43.
- Zlotogora J, Ben-Neriah Z, Abu Libdeh B, Zeigler M. High frequency of aspartylglucosaminuria among Palestinian Arabs. J Inher Metabol Disease 1997;20:799-802.

Ataxia microcephaly cataract syndrome

Autosomal recessive (MIM 208870)

In a highly inbred Arab family from the Galilee in which ataxia-telangiectasia was present, 3 individuals in two sibships had ataxia, hypotonia, microcephaly, and congenital cataracts with nystagmus. Mental retardation was also observed in 1 of the three and one individual was affected with both ataxia-telangiectasia and the AMC syndrome.

Epidemiology:

The syndrome has been reported only in **one village in the Galilee**.

Molecular genetics:

Unknown

References:

Ziv Y, Frydman M, Lange E, Zelnik N, Rotman G, Julier C, Jaspers NGJ, Dagan Y, Abeliovich D, Dar H, Borochowitz Z, Lathrop M, Gatti R A, Shiloh Y. Ataxia-telangiectasia: linkage analysis in highly inbred Arab and Druze families and differentiation from an ataxia-microcephaly-cataract syndrome. Hum Genet 1992; 88:619-626.

Ataxia telangiectasia

Autosomal recessive (MIM 208900)

The predominant clinical features are neurologic symptoms manifested in walking difficulties. The cerebral dysfunction is first manifested as ataxia and later by choreoathetosis, myoclonic jerking and oculomotor abnormalities. Telangiectasias, which are dilated blood vessels, are the second typical feature of this disorder, typically appear by 2-7 years first on the conjunctiva and later on exposed areas of the skin. Other dermatological abnormalities may also be present such as cafe au lait spots, vitiligo and loss of subcutaneous fat. Hormonal dysfunction is common and in females can be manifested by delayed or even absent secondary sexual development. Variable immunodeficiency is also found in patients affected with ataxia telangiectasia which may lead to recurrent upper respiratory and lung diseases. Most patients have normal intelligence. The patients have increased risk for cancers and more than 15% die from malignant diseases. Lymphomas are common in childhood while adult patients have increased incidence of gastric carcinoma, T cell lymphatic leukemia. The predominant cause of death is infections.

There are some indications that heterozygotes may have an increased risk to develop cancers when compared to the general population however, still no definite conclusion have been drawn.

Epidemiology:

Ataxia telangiectasia has been diagnosed in several Arab families in Israel and the territories and is found with an increased frequency among Arabs in several villages in the **Galilee** and a **Bedouin tribe in the Negev**.

Molecular genetics:

ATM gene (chromosomal locus 11q22-q23)

The disease is frequent in four villages from the Galilee in each of which the patients were homozygote for one mutation: among Christians [2284delCT], Muslim Arabs [497del17514] and Druze [1339C → T] and [6672delGG/delTACG]. In the Bedouin tribe the mutation is [7240delA].

References:

- Gilad S, Khosravi R, Harnik R, Ziv Y, Shkedy D, Galanty Y, Frydman M, Levi J, Sanal O, Chessa L, Smeets D, Shiloh Y, Bar-Shira A Identification of ATM mutations using extended RT-PCR and restriction endonuclease fingerprinting, and elucidation of the repertoire of A-T mutations in Israel. *Hum Mut* 1998;11:69-75
- Gilad S, Khosravi R, Shkedy D, Uziel T, Ziv Y et al.. Predominance of null mutations in ataxia telangiectasia. *Hum Mol Genet* 1996;5:433-439
- Ziv Y, Frydman M, Lange E, Zelnik N, Rotman G et al.. Ataxia-telangiectasia: linkage analysis in highly inbred Arab and Druze families and differentiation from an ataxia-microcephaly-cataract syndrome. *Hum Genet* 1992;88:619-626

Ataxia with oculomotor apraxia

Autosomal recessive (MIM 208920)

The predominant clinical features are of cerebellar ataxia, tremor, dysarthria, oculomotor apraxia, and motor peripheral neuropathy. Brain magnetic resonance imaging showed cerebellar atrophy and mild brainstem atrophy. Electromyography showed signs of axonal neuropathy. The two Arab children performed in the range of mild mental retardation

Epidemiology:

The disease has been diagnosed in two siblings from a Muslim Arab family living in a town from the small triangle.

Molecular genetics:

APTX gene (chromosomal locus 9p13.3)

The patients were homozygote for one mutation [W279X].

References:

Mahajnah M, Basel-Vanagaite L, Inbar D, Kornreich L, Weitz R, Straussberg R. Familial cognitive impairment with ataxia with oculomotor apraxia. *J Child Neurol.* 2005;20:523-525.

Ataxia with vitamin E deficiency

In 4 siblings of a consanguineous **Negev** Bedouin family with Friedreich ataxia phenotype, low serum vitamin E levels without other indicators of fat malabsorption were detected. Although age of onset and some of the clinical features were alike in all 4 patients, the electrophysiological parameters were markedly abnormal in 2, but normal in the other 2. Erythrocytes reveal both membranous and intracellular evidence of oxidative damage.

Vitamin E administration in pharmacological doses improved the neurological condition in 2 patients and also corrected some of the patients' erythrocyte cell abnormalities.

References:

Shorer Z, Parvari R, Bril G, Sela BA, Moses S. Ataxia with isolated vitamin E deficiency in four siblings. *Pediatr Neurol* 1996;15:340-343.

ATPase deficiency, nuclear encoded

Autosomal recessive (MIM 604273)

The patients usually present prenatally or in the first days of life. In utero presentation includes oligohydramnios, myocardial thickening and IUGR. Most patients present after birth with signs of hypertrophic cardiomyopathy having a fulminant course including acidosis, encephalopathy and organs failure culminating in early death. Other have a less severe presentation. Urinary 3 MGA excretion is an important biochemical marker and may be intermittent. Enzymatic OXPHOS activities in the muscle reveal deficiency in the activity of complex V in the muscle mitochondria.

Epidemiology:

The disorder has been reported in several Muslim patients one Bedouin family from the Negev and one family from the region of **Jerusalem**.

Molecular Genetics:

TMEM70 (chromosomal locus 8q21.11)

Several mutations were reported in the TMEM70 gene. The mutations c.366A >T (p. Y112X) and c.578-579delCA in two different families from the same Arab town; c.238C/T, p.R80X in a Bedouin family from the Negev. The mutation c.316+1G>T was found in a family from east Jerusalem

References:

Spiegel R, KhayatM, Shalev SA, Horovitz Y, Mandel H, HersHKovitz E, Barguthy F, Shaag A, Saada A, Korman SH, Elpeleg O, Yatsiv I. TMEM70 mutations are a common cause of nuclear encoded ATP synthase assembly defect: further delineation of a new syndrome J Med Genet 2011;48:177-182.

Atrichia, with papular lesions

Autosomal recessive (MIM 209500)

Inherited universal alopecia without ectodermal defects is very rare. Among the heritable form of alopecia, atrichia with papular lesions is characterized by hair loss soon after birth and several years later by the development of a diffuse papular rash over the entire skin surface.

Epidemiology:

The disorder has been reported in several patients from two large kindreds one from a village in the **Galilee** one from Haifa and several families from the region of **Jerusalem** and 5 families from the territories.

Molecular Genetics:

Hairless gene, HR (chromosomal locus 8p21.2)

The disorder is caused by mutations in the hairless gene was reported: a single base deletion [343delC] in the Galilee, in the region of Jerusalem [V1056M], [16bp duplication]] and a 22bp deletion in exon 3 [1256delC; 1261del21]. In the family from Haifa G to a transition in the hairless gene was found [D1012N]. In several families families from Israel and from the territories a deletion in exon 9 of the hairless gene was found [2147delC].

References:

- Klein I, Bergman R, Indelman M, Sprecher E. A novel missense mutation affecting the human hairless thyroid receptor interacting domain 2 causes congenital atrichia. *J Invest Dermatol* 2002;119:920-902
- Sprecher E, Bergman R, Szargel R, Fridman-Birnbaum R, Cohen N. Identification of a genetic defect in the hairless gene in atrichia with papular lesions: evidence for phenotypic heterogeneity among inherited atrichias. *Am J Hum Genet* 1999;64:1323-1329.
- Yip L, Horev L, Sinclair R, Zlotogorski A. Atrichia with papular lesions: a report of three novel human hairless gene mutations and a revision of diagnostic criteria. *Acta Derm Venereol.* 2008;88:346-349.
- Zlotogorski A, Ahmad W, Christiano AM. Congenital atrichia in five Arab Palestinian families resulting from a deletion mutation in the human hairless gene. *Hum Genet* 1998; 103:400-404.
- Zlotogorski A, Hochberg Z, Mirmirani P, Metzker A, Ben-Amitai D, Martinez-Mir A, Panteleyev AA, Christiano AM. Clinical and pathologic correlations in genetically distinct forms of atrichia. *Arch Dermatol.* 2003; 139:1591-1596.
- Zlotogorski A, Panteleyev AA, Aita VM, Christiano AM. Clinical and molecular diagnostic criteria of congenital atrichia with papular lesions. *J Invest Dermatol* 2002; 118:887-890.

Bardet-Biedel syndrome

Autosomal recessive (MIM 209500)

The cardinal features of the disorder are retinal dystrophy, obesity, mental retardation, polydactyly and hypogonadism. Both intra and inter familial variability has been reported in the syndrome in particular as for the degree of retardation, the obesity, the reproductive dysfunction and abnormalities of the renal system. It seems that almost all the patients with BBS present with some structural and functional renal abnormalities, when severe renal impairment is present in 15 to 50% of the patients.

Epidemiology:

The disease is relatively frequent among Arabs. In Israel as well as in Kuwait the incidence of BBS is particularly high among the **Bedouins**

Molecular genetics:

BBS2 gene (chromosomal locus 16q21)

All the Bedouin patients from a tribe in the Negev were homozygotes for [V75G]

BBS4 gene (chromosomal locus 15q22.3-q23)

All the Bedouin patients from a tribe in the Negev were found to be homozygotes [R295P]. In another Arab patient a deletion of exons 3 and 4 was found in homozygosity.

BBS3 gene (chromosomal locus 3p13-p12)

In another Bedouin tribe of the Negev, patients were found to be homozygotes [R122X].

BBS7 (chromosomal locus 4q27)

A Muslim patient from the Galilee was found homozygote for [E596K]

B1 gene, BBS9 (chromosomal locus 7p14)

A Druze patient from the Galilee was found homozygote for [IVS 17+1G>A]

TRIM32 gene, BBS11 (chromosomal locus 9q33.1)

In a Bedouin family from the Negev the patients were homozygous a missense mutation

References:

- Chiang AP, Nishimura D, Searby C, Elbedour K, Carmi R et al. Comparative Genomic Analysis Identifies an ADP-Ribosylation Factor-like Gene as the Cause of Bardet-Biedl Syndrome (BBS3). *Am J Hum Genet.* 2004;16:475-484.
- Harville HM, Held S, Diaz-Font A, Davis EE, Diplas BH, Lewis RA, Borochowitz ZU, Zhou W, Chaki M, MacDonald M, Kayserili H, Beales PL, Katsanis N, Otto E, Hildebrandt F. Identification of 11 Novel Mutations in 8 BBS Genes by High-Resolution Homozygosity Mapping. *J Med Genet* 2010;47:262-267. Epub 2009 Sep 24
- Nishimura DY, Searby CC, Carmi R, Elbedour K, van Maldergem L, Fulton AB, Lam BL et al. Positional cloning of a novel gene on chromosome 16q causing Bardet Biedel syndrome (BBS2). *Hum Mol Genet* 2001; 10:865-874.
- Nishimura DY, Swiderski RE, Searby CC, Berg Amanda EM, Ferguson L et al. Comparative genomics and gene expression analysis identifies BBS 9, a new Bardet-Biedl syndrome gene. *Am J Hum Genet* 2005; 77:1021-1033.
- Chiang P, Beck JS, Yen HJ, Tayeh MK, Scheetz TE et al. Homozygosity mapping with SNP arrays identifies *TRIM32*, an E3 ubiquitin ligase, as a Bardet-Biedl syndrome gene (*BBS11*) *PNAS* 2006;103:6287-6292.

Bartter syndrome, infantile variant with sensorineural deafness

Autosomal recessive (MIM 241200)

Bartter syndrome is characterized clinically by normotensive hyperreninism, hyperaldosteronism and hypokalemic hypochloremic metabolic alkalosis. Renal biopsy shows juxtaglomerular hyperplasia and the renal prostaglandin metabolism is up regulated. An infantile variant of the syndrome has been reported which is inherited as an autosomal recessive trait. Usually it causes maternal polyhydramnion, premature birth and post natal polyuria with severe salt loss and failure to thrive. Some infants have also hypercalciuria.

Epidemiology:

Several children affected with infantile Bartter syndrome with congenital sensorineural deafness were diagnosed in an extended **Bedouin tribe from the Negev**.

Molecular genetics:

BSND gene (chromosomal locus 1p31)

All the Bedouin patients have a same mutation [G28A].

References:

Birkenhager Otto E, Schurmann MJ, Vollmer M, Ruf EM, Maier-Lutz I et al. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. *Nature Genetics* 2001;29:310-314.

Landau D, Shalev H, Ohaly M, Carmi R. Infantile variant of Bartter syndrome and sensorineural deafness: a new autosomal recessive disorder. *Am J Med Genet* 1995; 59:454-459.

Bartter and Gitelman syndrome

Autosomal recessive (MIM 241200 and MIM263800)

Bartter syndrome, is as an autosomal recessive disorder featuring hypokalemic metabolic alkalosis with salt wasting. There is least 2 subsets, Gitelman syndrome and Bartter syndrome.

Features typical of Gitelman syndrome include late age of presentation, normal growth, hypomagnesemia, hypermagnesiuria and hypocalciuria (urinary calcium/creatinine mmol/mmol <0.15). Features typical of Bartter syndrome include early age of presentation (<1 year), polyuria/dehydration, growth retardation, hypercalciuria and nephrolithiasis.

Molecular genetics and Epidemiology:

CLCNKB gene (chromosomal locus 1p36)

Several patients affected with either with Bartter or Gitelman syndrome were diagnosed in an extended **Bedouin family** from two close **villages in the Lower Galilee**. All have a same mutation in the CLCNKB gene [R438H]. At least one other mutation has been found among an Arab patient from the Galilee.

References:

Zelikovic I, Szargel R, Hawash A, Labay V, Hatib I, Cohen N, Nakhoul F.

A novel mutation in the chloride channel gene, CLCNKB, as a cause of Gitelman and Bartter syndromes. *Kidney Int* 2003;63:24-32.

Biotinidase deficiency

Autosomal recessive (MIM 253260)

The most frequent initial symptoms are seizures with or without other neurological manifestations such as hypotonia, ataxia, hearing loss and optic atrophy. Other symptoms are dermatologic such as a skin rash and alopecia. Ketoacidosis and organic aciduria are also features of the disorder. If untreated the symptoms become progressively worse and coma and death may occur.

The children cannot not cleave and therefore recycle biotin. If the children are not supplemented with free biotin they become biotin dependent which in turn result in decreased activities of the biotin dependent carboxylases and the subsequent accumulation of toxic metabolites causing the clinical symptoms. Treatment with massive doses of biotin reverses the symptoms in particular if it is early enough but often some residual neurological damage remains.

Epidemiology:

The disease has been diagnosed among Muslim Arabs in 2 villages in the **Galilee** (Mandel H).

Molecular genetics:

BTB gene (chromosomal locus 3p25)

A deletion/ insertion is common causing profound biotinidase deficiency. A mutation [G₁₀₀→A Gly34Ser] has been characterized in unrelated patients one of them Israeli Arab from the Galilee.

A 393C deletion was found in two patients.

References:

Pomponio RJ, Reynolds TR, Mandel H, Admoni O, Melone PD, Buck GA, Wolf B. Profound biotinidase deficiency caused by a point mutation that creates downstream cryptic 3' splice acceptor site within an exon of the human biotinidase gene. *Hum Mol Genet* 1997;6:739-745.

Wolf B, K. Jensen K, Hüner G, Demirkol M, Baykal T, Divry P, Rolland MO, Perez-Cerdá C, Ugarte M, Straussberg R, Basel-Vanagaite L, Baumgartner ER, Suormala T, Scholl S, Das AM, Schweitzer S, Pronicka E, Sykut-Cegielska J. Seventeen novel mutations that cause profound biotinidase deficiency. *Mol Genet Metabol* 2002;77:108-111

Brittle cornea syndrome

Autosomal recessive (OMIM 229200)

The brittle cornea syndrome is a generalized connective tissue disorder including blue sclera, brittle cornea and hyperextensibility of joints. All the patients have blue sclera and corneal involvement. In all cases the cornea are thin and brittle and "spontaneous" corneal perforations may be devastating complications and should be prevented if possible. Joint laxity is variable, and in some cases it may lead to severe congenital dislocation of hips and vertebral instability. Other symptoms, which are often present in the patients, are dentinogenesis imperfecta and hearing defects.

Molecular genetics and epidemiology:

ZNF469 (Chromosomal locus 6q24)

The disease was reported in a two generation Muslim Arab family from the region of Jerusalem. The mutation was a single-nucleotide deletion at position 9527 (9527 delG).

References

- Abu A, Frydman M, Marek D, Pras E, Nir U, Reznik-Wolf H, Pras E. Deleterious mutations in the Zin-finger 469 gene case brittle cornea syndrome. *Am J Hum Genet.* 2008; 82:1217-1222.
- Zlotogora J, BenEzra D, Cohen E and Cohen T. Syndrome of brittle cornea, blue sclera and joint hyperextensibility. *Am J Med Genet* 1990;36:269-272.

Brachydactyly type A2

Autosomal recessive (MIM 112600)

Brachydactyly is a group of inherited malformations characterized by shortening of the digits due to abnormal development of the phalanges and/or the metacarpals, usually manifest as autosomal dominant traits. In a consanguineous family severe brachydactyly segregated in an autosomal recessive mode of heredity.

Epidemiology:

The disease was diagnosed among in a Bedouin tribe. Heterozygous carriers showed no signs of the phenotype.

Molecular genetics:

Bone morphogenetic protein receptor 1B (BMPR1B) gene (chromosomal locus 4q23-q24)

a novel missense mutation, G377A, resulting in substitution of cysteine to tyrosine at the conserved amino acid 34 (C34Y) in the extracellular ligand binding domain of BMPR1B. All affected individuals were homozygous for the mutation.

References:

Agamy O, Abuelaish I, Ofir R, Birk OS. Autosomal recessive severe Brachydactyly caused by a novel BMPR1B mutation. ASHG 2006.

Calcinosis, tumoral with hyperphosphatasemia.

Autosomal recessive (MIM 211900)

The major clinical features are: heterotopic calcification, hyperphosphatemia, unresponsiveness to parathyroid hormone, and elevated renal tubular maximum for phosphate reabsorption. In order of frequency for the site of first lesions, hips, elbows, shoulders, and scapulae led the list. The patients have elevated serum phosphorus levels. Onset is in the first and second decades of life. Tumoral calcinosis is triggered by bleeding, followed by aggregation of foamy histiocytes. These, in turn, are transformed, with participation of collagenolysis, into cystic cavities lined by osteoclast-like giant cells and histiocytes, resulting in lesions resembling adventitious bursae. Movement and friction resulting from the periarticular location of the lesions were thought to be key to this transformation.

Hyperphosphatemia-hyperostosis syndrome (HHS) is a rare autosomal recessive metabolic disorder characterized by elevated serum phosphate levels and repeated attacks of acute, painful swellings of the long bones with radiological evidence of periosteal reaction and cortical hyperostosis. HHS shares several clinical and metabolic features with hyperphosphatemic familial tumoral calcinosis (HFTC).

Epidemiology:

The disease has been reported in two Druze closely related families and Muslim Arab families from Jerusalem (HHS).

Molecular genetics:

GALNT3 gene (chromosomal locus 2q24-q31)

In the Druze and Muslim Arab families the patients were homozygous for G to A transition at 1524+1

References:

- Frishberg Y, Topaz O, Bergman R, Behar D, Fisher D, Gordon D, Richard G, Sprecher E. Identification of a recurrent mutation in GALNT3 demonstrates that hyperostosis-hyperphosphatemia syndrome and familial tumoral calcinosis are allelic disorders. *J Mol Med.* 2005;83:33-38.
- Metzker A, Eisenstein B, Oren J, Samuel R. Tumoral calcinosis revised- common and uncommon features. Report of 10 cases and Review. *Eur J Pediatr* 1988 147:128-132.
- Topaz O, Shurman DL, Bergman R, Indelman M, Ratajczak P, Mizrachi M, Khamaysi Z, Behar D, Petronius D, Friedman V, Zelikovic I, Raimer S, Metzker A, Richard G, Eli Sprecher E.. Mutations in *GALNT3*, encoding a protein involved in O-linked glycosylation, cause familial tumoral calcinosis. *Nat Genet.* 2004;36:579-581.

Carbamoyl phosphatase synthetase deficiency

Autosomal recessive (MIM 237300)

Carbamoyl phosphate synthetase I deficiency is an autosomal recessive inborn error of metabolism of the urea cycle which causes hyperammonemia. Urea cycle disorders are characterized by the triad of hyperammonemia, encephalopathy, and respiratory alkalosis. An early onset and late onset forms have been described

Epidemiology and molecular genetics:

carbamoyl phosphate synthetase I CPS1 gene (chromosomal locus 2q35)

The disease has been diagnosed in several Druze patients from one village due to the founder mutation c.31265C>T. The disease was diagnosed in a Christian family with the mutation IVS29 1G>C.

Cardiomyopathy, dilated idiopathic

Autosomal dominant (MIM 188840)

Idiopathic dilated cardiomyopathy (DCM) is a major cause of heart failure and heart transplantation in young adults. In a large Muslim-Arab kindred from Galilee with familial DCM inherited as an autosomal dominant trait 13 affected individuals: 8 males and 5 females have been identified. Two were cardiac transplant recipients and 7 had symptomatic heart failure. None had skeletal myopathy.

Molecular genetics:

Titin I CPS1 gene (chromosomal locus 2q24.3)

An Adenine insertion at position 59014 creating a stop codon 4 bp down stream, predicting a truncated protein was characterized in all the patients.

References:

Yoskovitz G, Gramlich M, Freimark D, Thierfelder L, Lahat H, Reznik-Wolf H., Feinberg M S, Pras E, Arad M, Gerull B. A novel Titin mutation causing dilated cardiomyopathy was found in family from Galilee. Congress ESHG 2007

Cardiomyopathy dilated, neonatal isolated

Autosomal recessive (MIM 115200)

Idiopathic dilated cardiomyopathy (DCM) is a major cause of heart failure and heart transplantation in young adults. In a large Muslim-Bedouin kindred from Negev with familial DCM inherited as an autosomal recessive trait 15 affected individuals

The age of onset was between 30 weeks in utero to 10 years, one patient the father of affected children was asymptomatic. Nine of the 15 patients died at the age of 1 to 11 months .

Molecular genetics:

Succinate dehydrogenase flavoprotein SDHA gene (chromosomal locus 5)

A same mutation was found in homozygosity in all the patients c.1664G>A p.G55E

References:

Levitas A, Muhammad E, Harel G, Saada A, Caspi VC, Manor E, Beck JC, Sheffield V, Parvari R. Familial neonatal isolated cardiomyopathy caused by a mutation in the flavoprotein subunit of succinate dehydrogenase. *Eur J Hum Genet.* 2010;18:1160-1165.

Carnitine-acylcarnitine translocase deficiency

Autosomal recessive (MIM 212138)

Carnitine-acylcarnitine translocase CACT deficiency is a very rare autosomal recessive disease. The neonatal phenotype of CACT deficiency is characterized by hypoketotic hypoglycaemia, hyperammonaemia, cardiomyopathy and skeletal muscle weakness culminating in early death.

Epidemiology:

The disease has been reported one Bedouin family from the Negev the parents were first cousins.

Molecular genetics:

Carnitine-acylcarnitine translocase CACT gene (chromosomal locus 2q24-q31)

The patient was homozygous for [Q238R].

References:

Galron D, Birk OS, Kazanovitz A, Moses SW, HersHKovitz E. Carnitine-acylcarnitine translocase deficiency: identification of a novel molecular defect in a Bedouin patient. J Inherit Metab Dis. 2004;27:267-273.

Carnitine-palmitoyltransferase I deficiency

Autosomal recessive (MIM 255120)

CPT I deficiency is an autosomal recessive metabolic disorder of long-chain fatty acid oxidation characterized by severe episodes of hypoketotic hypoglycemia usually occurring after fasting or illness. Onset is in infancy or early childhood

Epidemiology and molecular genetics:

carnitine palmitoyltransferase IA gene CPT1A (chromosomal locus 11q13)

The disease has been diagnosed in two villages in several Druze patients due to the founder mutation D454G (Falik-Zaccai TC)

Carnitine Palmitoyl transferase II deficiency

Autosomal recessive (MIM 600649)

Whereas adults with deficiency of CPT II have a disorder characterized by exercise intolerance and myoglobinuria, the same deficiency in newborns is a generalized lethal disease with reduced CPT II activity in multiple organs, reduced concentrations of total and free carnitine, and increased concentrations of lipids and long-chain acylcarnitines. A lethal neonatal form and one with prenatal onset have been recognized. Infants with the severe infantile form of CPT II deficiency usually die young and have cardiac abnormalities..

Clinical manifestations of CPT II deficiency usually have their onset in adolescence or adulthood. Patients may suffer from recurrent episodes of rhabdomyolysis after prolonged exercise.

Epidemiology:

The disease has been reported in one Muslim Arab child affected with a severe form of the disease who died at the age of three months

Molecular genetics:

Carnitine palmitoyltransferase II gene CPTII (chromosomal locus 1p32)

The child was homozygous for [R503C].

References:

Spiegel R, Shaag A, Gutman A, Korman SH, Saada A, Elpeleg O, Shalev SA. Severe infantile type of carnitine palmitoyltransferase II (CPT II) deficiency due to homozygous R503C mutation. J Inherit Metab Dis. 2007;30:266.

Cataracts, autosomal recessive

Autosomal recessive (MIM 600429, 600929)

The cataracts are congenital and the affected individuals need operation before few months of age. The patients possessed the adult blood group phenotype. The null phenotype of blood group I, the adult i phenotype, results from a defect in the specific transferase that converts the structure of the antigen from linear to branched repeats of N-acetylglucosamine, which characterize blood group antigen i and I, respectively. The adult i phenotype was found to be associated with congenital cataract.

Epidemiology:

Autosomal cataracts have been diagnosed in several Muslim Arab families from one village in central Israel and in one family from another village located 40 kms from the first one. In addition, the disorder was reported in two extended unrelated Bedouin tribes.

Molecular genetics:

Transferase 2 gene (GCNT2) gene (Chromosomal locus 6p24-23).

All the Arab patients were homozygous for a G→A substitution in base 58 of exon-2, resulting in the formation of premature stop codons W328X, W326X, and W328X, of the GCNT2A, -B, and -C isoforms, respectively.

CRYBB1 gene (Chromosomal locus 22q11.2-q12.1).

In the two Bedouin tribes the affected were homozygous for delG168 in exon2

FYCO1 gene (Chromosomal locus 3p21-p22)

In three Muslim families from a same village the same mutation c.1546C>T (p.Gln516X) was characterized.

References:

- Chen J, Ma Z, Jiao X, Fariss R, Kantorow WL, Kantorow M, Pras E, Frydman M, Pras E, Riazuddin S, Riazuddin SA, Hejtmancik JF. Mutations in FYCO1 Cause Autosomal-Recessive Congenital Cataracts. *Am J Hum Genet.* 2011; 88:827-838.
- Cohen D, Bar-Yosef U, Levy J, Gradstein L, Belfair N, Ofir R, Joshua S, Lifshitz T, Carmi R, Birk OS. Homozygous CRYBB1 Deletion Mutation Underlies Autosomal Recessive Congenital Cataract. *Invest Ophthalmol Vis Sci.* 2007;48:2208-2213.
- Pras E, Raz J, Yahalom V, Frydman M, Garzozzi HJ, Pras E, Hejtmancik JF. A Nonsense Mutation in the Glucosaminyl (N-acetyl) Transferase 2 Gene (GCNT2): Association with Autosomal Recessive Congenital Cataracts. *Invest Ophthalmol Vis Sci.* 2004;45:1940-1945.

Cerebellar-Retinal Degeneration- infantile

Autosomal recessive (MIM 100850)

The course is characterized by failure to acquire developmental milestones and culminated in profound psychomotor retardation and progressive visual loss, including optic nerve and retinal atrophy. Despite the debilitating state, the disease was compatible with survival of up to 18 years. Laboratory investigations were normal, but the oxidation of glutamate by muscle mitochondria was slightly reduced. Serial brain MRI displayed progressive, prominent cerebellar atrophy accompanied by thinning of the corpus callosum, dysmyelination, and frontal and temporal cortical atrophy.

Epidemiology:

The disease was reported in two Muslim Arabs families.

Molecular genetics:

OCA2 gene (chromosomal locus 22q13.2).

The patients were homozygous for a same Ser112Arg mutation.

References:

Spiegel R, Pines O, Ta-Shma A, Burak Et, Shaag A, Halvardson J, Edvardson S, Mahajna M, Zenvirt S, Saada A, Shalev S, Feuk L, Elpeleg O. Infantile Cerebellar-Retinal Degeneration Associated with a Mutation in Mitochondrial Aconitase, ACO2. Am J Hum Genet. 2012;90 518-523

Cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma (CEDNIK syndrome)

Autosomal recessive (MIM 609528)

A neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma (CEDNIK syndrome).

The patients were born at term and presented with a progressive microcephaly with facial dysmorphism. Palmoplantar keratoma and ichthyosis appear between 5 and 11 months of age with progressive worsening. By the age of 8-15 months psychomotor retardation become evident and major developmental milestones like sitting are not attained. Mild sensorineural deafness was present in some of the patients.

Epidemiology and molecular genetics:

SNAP29 gene (chromosomal locus 22q11.2).

The disease was reported among Muslim Arabs from two close villages in the **western Galilee**. The patients were homozygous for a same one bp deletion 220delG.

References:

Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M, Rapaport D, Goldsher D, Indelman M, Topaz O, Chefetz I, Keren H, O'Brien TJ, Bercovich D, Shalev S, Geiger D, Bergman R, Horowitz M, Mandel H. A Mutation in SNAP29, Coding for a SNARE Protein Involved in Intracellular Trafficking, Causes a Novel Neurocutaneous Syndrome Characterized by Cerebral Dysgenesis, Neuropathy, Ichthyosis, and Palmoplantar Keratoderma. *Am J Hum Genet* 2005;77 242-251.

Cerebrotendinous xanthomatosis

Autosomal recessive (MIM 213700)

The disease is variable in its symptoms as well as the age of onset. Juvenile cataracts are frequent and are often the presenting symptom of the disease. Tendon xanthomas may be present in the second decade but more often develop in the third and fourth decade. The most common site of xanthomas is the Achilles tendons, tibial tuberosities, extensor tendons of the fingers and the triceps. Most patients have low intelligence or are mentally retarded. They develop a progressive neurological disease including progressive spasticity with ataxia and in general the patient becomes incapacitated in the fourth to fifth decade.

The major symptoms of the disease are due to the generalized accumulation of cholestanol and cholesterol in almost every tissue including the nervous system. The basic defect is in sterol 27-hydroxylase a mitochondrial cytochrome P-450. The diagnosis can be done either by molecular screening for mutations in the 27-OH gene or by determining serum cholestanol levels using gas chromatography.

Presymptomatic diagnosis and treatment may allow the prevention of most symptoms of the disease.

Epidemiology and mMolecular genetics:

CYP27 gene (chromosomal locus 2q33-qter).

The disease is frequent in a Druze village in the **western Galilee**. All the patients from the Druze village were homozygous for a same deletion in Cytosine 376.

References:

Leitersdorf E, Safadi R, Meiner V, Reshef A, Bjorkhem I, Friedlander Y, Morkos S, Berginer M. Cerebrotendinous xanthomatosis in the Israeli Druze: molecular genetics and phenotypic characteristics. *Am J Hum Genet* 1994;55:907-915.

Ceroid lipofuscinosis, neuronal type 8

Autosomal recessive (MIM 600143)

The neuronal ceroid lipofuscinoses (NCL; CLN) are a clinically and genetically heterogeneous group of neurodegenerative disorders characterized by the intracellular accumulation of autofluorescent lipopigment storage material in different patterns ultrastructurally. The lipopigment patterns observed most often in CLN8 comprise mixed combinations of 'granular,' 'curvilinear,' and 'fingerprint' profiles.

In the so-called Turkish variant of late-infantile CLN the mean age at disease onset is 5 years with seizures or motor impairment as the most common presenting symptom. As the disease progresses, mental regression, myoclonus, speech impairment, loss of vision, and personality disorders develops, and most of the patients become nonambulatory within 2 years after onset. The features distinguishing the Turkish variant from CLN2 and CLN3 included a more severe course regarding seizures, the presence of condensed fingerprint profiles on electron microscopic examination of lymphocytes, and lack of vacuolated lymphocytes

Epidemiology and molecular genetics:

The CLN8 gene (chromosomal locus 8pter-p22)

In one large Muslim Arab family three patients were reported with a 763C>G mutation. While one patient presented with a severe phenotype with a rapidly progressive disease when 3 years after the onset (at the age of 5 years) he lost his mobility and manifested dementia seizures and profound visual loss, the other two affected were considerably less affected with a very slowly progressive disease.

References:

- Mahajna M, Zelnik N. Phenotypic heterogeneity in consanguineous patients with a common CLN8 mutation. *Pediatr Neurol.* 2012;47:303-305.
- Zelnik N, Mahajna M, Iancu TC, Sharony R, Zeigler M. A novel mutation of the CLN8 gene: is there a Mediterranean phenotype? *Pediatr Neurol.* 2007; 36:411-413.

Chanarin-Dorfman syndrome

Autosomal recessive (MIM 275630)

Chanarin-Dorfman syndrome also referred as 'neutral lipid storage diseases with ichthyosis' is a non lysosomal inborn error of neutral lipid metabolism. The clinical phenotype includes ichthyosis liver steatosis with hepatomegaly with muscle weakness (myopathy) ataxia, hearing loss subcapsular cataract and sometimes mental retardation. The diagnosis is suspected because of the presence of lipid droplets in granulocytes.

The disease was found in several patients of a consanguineous family from the triangle.

Epidemiology and Molecular genetics:

ABHD5 gene (chromosomal locus 3p21).

In one family the patients were homozygous for c.506ins101; in the other family for p.Arg312Ter

References:

Samuelov L, Fuchs-Telem D, Sarig O, Sprecher E. An exceptional mutational event leading to Chanarin Dorfman syndrome in a large consanguineous family. *Br J Dermatol.* 2011;164:1390-1392.

Elitzur S1, Yacobovich J, Dgany O, Krasnov T, Rosenbach Y, Tamary H. From blood smear to lipid disorder: a case report. *J Pediatr Hematol Oncol.* 2013;35:e329-31.

Chronic granulomatous disease

Autosomal recessive (MIM 233710)

Inherited disorder of phagocytes in which defective production of microbicidal oxydants lead to severe infections.

The diagnosis is done by the absence of NBT reduction by stimulated neutrophils.

Molecular genetics:

The syndrome is heterogenous and is caused by mutations in any of 4 genes encoding components of nicotinamide adenine dinucleotide phosphate (reduced form; NADPH) oxidase, the multisubunit enzyme that produces the precursor of these oxidants, superoxide

*P67-phox (chromosomal locus 1q25).***MIM 233710**

In one family from Jordan and one Palestinian family the same mutation was found in homozygosity: del 1169-1173 leading to a stop codon at 401 [IVS4DS, G-A, +1]. In another family with several affected individuals a nonsense mutation C304T (Arg102 > stop) was characterized

*CYBA, p22-phox (chromosomal locus 22q13.1).***MIM 601488**

In an Arabic family a missense mutation C164G was characterized.

In a Israeli Arab family the patient was homozygous for a missense mutation G71A (Gly24 > Glu) also found in an Yemenite Jewish family.

References:

Patino PJ, Rae J, Noack D, Erickson R, Ding J, de Olarte DG, Curnutte JT. Molecular characterization of autosomal recessive chronic granulomatous disease caused by a defect of the nicotinamide adenine dinucleotide phosphate (reduced form) oxidase component p67-phox. Blood 1999;94:2505-2514.

Wolach B, Gavrieli R, de Boer M, Gottesman G, Ben-Ari J, Rottem M, Schlesinger Y, Grisaru-Soen G, Etzioni A, Roos D. Chronic granulomatous disease in Israel: Clinical, functional and molecular studies of 38 patients. Clin Immunol. 2008; 129:103-114.

Citrullinemia type II, neonatal onset

Autosomal recessive (MIM 605814)

Patients with citrullinemia type II have a neonatal-onset and present between 1 and 5 months of age with cholestatic jaundice. Liver histology show fatty tissue without evidence of giant cell hepatitis, the usual finding in most forms of transient neonatal jaundice.

Epidemiology and Molecular genetics

SLC25A13 (chromosomal locus 7q21.3)

A patient from a Muslim Arab family in Jerusalem was homozygous for a duplication of exon 15 (139 bp) resulting in a frame shift at codon 532 and the addition of 28 new AA. In two Muslim Arab families one from the North of the country the other from the lower Galilee, the patients were homozygous for L598R (T1793G).

References:

- Ben-Shalom E, Kobayashi K, Shaag A, Yasuda T, Gao HZ, Saheki T, Bachmann C, Elpeleg O. Infantile citrullinemia caused by citrin deficiency with increased dibasic amino acids. *Mol Genet Metab.* 2002;77:202-208.
- Luder AS, Tabata A, Iijima M, Kobayashi K, Mandel H. Citrullinaemia type 2 outside east Asia-Israeli experience. *J Inheret Metab dis* 29 (supplement 1) 59.

Cleft lip/palate ectodermal dysplasia, CLPED1 (Zlotogora-Ogur syndrome)

Autosomal recessive (MIM 225060)

In a family from the region of Jerusalem a syndrome including cleft lip and palate, syndactyly of the fingers (3 and 4) and feet with pli torti and hydrotic ectodermal dysplasia was reported. The proband was mentally retarded and his sister died before the age of one year. Later the variability of the syndrome was demonstrated in particular the absence of mental retardation in many affected patients.

Epidemiology

A single Muslim Arab family

Molecular genetics

Nectin-1, an immunoglobulin-related transmembrane cell-cell adhesion molecule
PVRL1 (chromosomal locus 11q23)

The Arab patient was homozygous for a single base deletion in codon Gly 323 resulting in a frame shift.

References:

- Suzuki K, Hu D, Bustos T, Zlotogora J, Richieri-Costa A, Helms J A, Spritz RA. Mutations of PVRL1 cell-cell adhesion molecule/Herpesvirus receptor gene in cleft lip/palate-ectodermal dysplasia. *Nature Genet* 2000 25:427-430.
- Zlotogora J. Syndrome of the month: Syndactyly, ectodermal dysplasia and cleft lip/palate. *J Med Genet* 1994;31:957-959.
- Zlotogora J, Zilberman Y, Tenenbaum A, Wexler MR. Cleft lip and palate, pili torti, malformed ears, partial syndactyly of fingers and toes and mental retardation. A new syndrome? *J Med Genet* 1987;24:291-293.

Cockayne syndrome

Autosomal recessive (MIM216400)

The characteristics are dwarfism, precociously senile appearance, pigmentary retinal degeneration, optic atrophy, deafness, marble epiphyses in some digits, sensitivity to sunlight, and mental retardation. Disproportionately long limbs with large hands and feet and flexion contractures of joints are usual skeletal features. Knee contractures result in a 'horseriding stance'. Death from early atherosclerosis often occurs.

The ocular findings include strabismus, cataracts and nystagmus. Visual acuity is relatively well preserved despite advanced retinal pigmentary changes.

Fibroblasts from the patients show a defect in the repair of UV-induced thymine dimer lesions; the fibroblasts are unable to remove thymine dimer lesions from their DNA and have a severe reduction of RNA synthesis rates after UV irradiation

Molecular genetics and epidemiology:

There are multiple causes of the Cockayne syndrome, or a phenotype closely resembling Cockayne syndrome,

Classic type I

CSA, CKN1 gene, chromosome 5.

Several Christian Arab patients from were homozygous for tyr322stop c.966 C>A

The mutation is frequent among Israeli Christian Arabs(1:42 carrier in almost 4000 individuals screened)

CSB gene ERCC6, chromosome 10q11.

In a large Druze kindred from a village in the Galilee several patients were homozygous for a mutation in CSB [c.1034-1035 insT]. This mutation has been found in 1:15 healthy individuals from the same village.

References:

Falik-Zaccai TC, Laskar M, Kfir N, Nasser W, Slor H, Khayat M. Cockayne Syndrome Type II in a Druze isolate in Northern Israel in association with an insertion in ERCC6. *Am J Med Genet* 2008;146A:1423-1429

Khayat M1, Hardouf H, Zlotogora J, Shalev SA. High carriers frequency of an apparently ancient founder mutation p.Tyr322X in the ERCC8 gene responsible for Cockayne syndrome among Christian Arabs in Northern Israel. *Am J Med Genet A*. 2010;152A:3091-4.

McDaniel LD, Legerski R, Lehmann AR, Friedberg EC, Schultz RA. Confirmation of homozygosity for a single nucleotide substitution in a Cockayne syndrome patient using monoallelic mutation in somatic cell hybrids. *Hum Mut* 1997; 10:317-321.

Lehmann AR, Thompson AF, Harcourt SA, Stefanini M, Norris PG. Cockayne syndrome: correlation of clinical features with cellular sensitivity to UV irradiation. *J Med Genet* 1993;30:679-682

Complement C7 deficiency

Autosomal recessive (MIM 217070)

Increased tendency to meningococcal disease.

Epidemiology:

C7 deficiency was found to be frequent in one village from the lower Galilee.

Molecular genetics:

C7 (chromosomal locus 5p13)

All the patients examined shared a same haplotype and had a same mutation p.G1135C

References

Behar D, Scchlesinger M, Halle D, Ben-Ami H, Edoute Y, Shahar E, Kasis I, Shihab S, Elstein D, Zimran A, Mandel H. C7 complement defidency in an Israeli Arab village. Am J Med Genet 2002;110:25-29

Complex 1 deficiency, mitochondrial respiratory chain

Autosomal recessive (MIM 252010)

Five clinical phenotypes are frequently seen in patients with complex I deficiency: severe neonatal lactic acidosis, Leigh's disease, cardiomyopathy-encephalopathy, hepatopathy-tubulopathy, and leukodystrophy with macrocephaly

Epidemiology and Molecular genetics:

NDUFS2 gene (chromosomal locus 1q23)

In two Christian Arab families from the Galilee, the patients are homozygous for the same mutation 1237 T>C

NDUFA12 gene (chromosomal locus 12q22)

The disorder was diagnosed in three unrelated families, one Bedouin from the Negev. While the clinical presentation was different, the patients were all homozygous for the same mutation IVS15G>A.

NDUFAF3 gene (chromosomal locus 3p21.31)

The disorder was diagnosed in one muslim family from the center of Israel, the patients were all homozygous for G77R, in another Muslim family from the Palestinian Authority territories the patients were homozygous for R122P

References

- Berger I, HersHKovitz E, Shaag A, Edvardson S, Saada A, Elpeleg O. Mitochondrial complex I deficiency caused by a deleterious NDUFA11 mutation. *Ann Neurol*. 2008;63:405-408
- Loeffen J, Elpeleg O, Smeitink J, Smeets R, Stockler-Ipsiroglu S, Mandel H, Sengers R, Trijbels F, van den Heuvel L. Mutations in the complex I NDUFS2 gene of patients with cardiomyopathy and encephalomyopathy. *Ann Neurol*. 2001;49:195-201
- Saada A, Vogel RO, Hoefs SJ, van den Brand MA, Wessels HJ, Willems PH, Venselaar H, Shaag A, Barghuti F, Reish O, Shohat M, Huynen MA, Smeitink JA, van den Heuvel LP, Nijtmans LG. Mutations in NDUFAF3 (C3ORF60), encoding an NDUFAF4 (C6ORF66)-interacting complex I assembly protein, cause fatal neonatal mitochondrial disease. *Am J Hum Genet*. 2009;84:718-827. Epub 2009 May 21

Complex III deficiency, mitochondrial respiratory chain

Autosomal recessive (MIM 124000)

In a large consanguineous inbred Israeli Bedouin the severe neuromuscular phenotype affected a total of 25 individuals. Twenty of the affected individuals were available for detailed clinical and molecular analyses. The abnormal phenotype was markedly uniform and consisted of severe psychomotor retardation and extrapyramidal signs. Affected individuals seemed normal at birth without any dysmorphic features. During the first few months of life, the prominent clinical feature was failure to achieve normal developmental milestones. By age 2–3 years, extrapyramidal signs were evident in all patients, presenting with dystonic postures, athetoid movements, and ataxia. All affected individuals had severe mental retardation. Neurological examination demonstrated restlessness, marked global dementia, and severe defects in verbal receptive communication and near total absence of expressive communication skills, with inability to express any words at any age. Mild axial hypotonia, increased tone in the upper and lower limbs, and increased deep tendon reflexes in all four extremities with inability to walk unsupported were evident in all patients. Cranial nerves were intact and ophthalmologic exam was normal. The phenotype is not lethal, with some affected individuals surviving well into their thirties. Electroencephalogram (EEG) demonstrated nonspecific mild generalized slowing. Brain magnetic resonance imaging (MRI) done in five patients showed bilateral symmetric abnormal findings in the basal ganglia (Figure 2), with increased density in the putamen and decreased density and size of the caudate and Globus pallidum nuclei. There was no involvement of the brain-stem area.

Molecular genetics:

UQCRCQ complex III subunit VII, 9.5 kDa. *gene (chromosomal locus 8q22)*

All the patients were homozygous for a c.208C → T mutation in exon 2, replacing serine at position 45 by phenylalanine (p.Ser45Phe) in the encoded protein)

References

Barel O, Shorer Z, Flusser H, Ofir R, Narkis G, Finer G, Shalev H, Nasasra A, Saada A, irk OS. Mitochondrial Complex III Deficiency Associated with a Homozygous Mutation in UQCRCQ. *Am J Hum Genet* 2008; 83:193-199.

Complex hereditary spastic paraparesis

Autosomal recessive (MIM 609927)

All the patients presented with, developmental and motor delay from the first or second year of life, followed by unsteadiness in standing, and difficulties in walking. The children presented with spasticity in the lower limbs that progressed to the upper extremities, requiring recurrent physiotherapy and ligament lengthening operations.

All patients presented mild to moderate delays in cognition and speech and marked kyphosis

Molecular genetics:

Vps37A gene (chromosomal locus 8p22)

All the patients were homozygous for a c.1146A>T mutation (p.K382N)

References

Zivony-Elboum Y, Westbroek W, Kfir N, Savitzki D, Shoval Y, Bloom A, Rod R, Khayat M, Gross B, Samri W, Cohen H, Sonkin V, Freidman T, Geiger D, Fattal-Valevski A, Anikster Y, Waters AM, Kleta R, Falik-Zaccai TC. A founder mutation in *Vps37A* causes autosomal recessive complex hereditary spastic paraparesis. *J Med Genet.* 2012;49:462-472.

Cone-rod dystrophy

Autosomal recessive (MIM 604116)

Within the family of retinal dystrophy the cone-rod dystrophy phenotype is a specific form of degeneration. The cone degeneration appears early in life with central involvement of the retina followed by degeneration of rods several years later. The main symptoms at the disease onset are decrease visual acuity loss of color discrimination and photophobia. The b wave of the photopic ERG is severely reduced although the b wave of the scotopic ERG is still normal. As the disease progresses, nyctalopia, progressive peripheral visual field deficit and decreasing scotopic ERG are observed.

Molecular genetics and Epidemiology:

ABCA4 gene (chromosomal locus 1p21-q13)

Three different mutations were found in one large Christian kindred from the Galilee, with a progressive severe Stargardt like disease c.5460+1G>A, c.5882G>A, c.3607G>A. In a Muslim Arab kindred living in a village near Jerusalem one founder mutation was characterized c.4254—15del 23 and another mutation p.Cys1150del in one allele.

ADAM9 gene (chromosomal locus 8p11.23)

In one Muslim Arab family from Jerusalem, the mutation c.411-8A>G was found in homozygosity.

PROM1 gene (chromosomal locus 4p15.3)

In one Christian Arab family from the center, the mutation c.1349insT was found in homozygosity.

References

- Beit-Ya'acov A, Mizrahi-Meissonnier L, Obolensky A, Landau C, Blumenfeld A, Rosenmann A, Banin E, Sharon D. Homozygosity for a novel ABCA4 founder splicing mutation is associated with progressive and severe Stargardt-like disease. *Invest Ophthalmol Vis Sci.* 2007;48:4308-4314.
- Ducroq D, Shalev S, Habib A, Munnich A, Kaplan J, Rozet JM. Three different ABCA4 mutations in the same large family with several consanguineous loops affected with autosomal recessive cone-rod dystrophy. *Eur J Hum Genet.* 2006;14:1269-1273.
- Parry DA, Toomes C, Bida L, Danciger M, Towns KV, McKibbin M, Jacobson SG, Logan CV, Ali M, Bond J, Chance R, Swendeman S, Daniele LL, Springell K, Adams M, Johnson CA, Booth AP, Jafri H, Rashid Y, Banin E, Strom TM, Farber DB, Sharon D, Blobel CP, Pugh EN Jr, Pierce EA, Inglehearn CF. Loss of the metalloprotease ADAM9 leads to cone-rod dystrophy in humans and retinal degeneration in mice. *Am J Hum Genet.* 2009;84:683-689. Epub 2009 Apr 30.
- Pras E, Abu A, Rotenstreich Y, Avni I, Reish O, Morad Y, Reznik-Wolf H, Pras E. Cone-rod dystrophy and a frameshift mutation in the PROM1 gene. *Mol Vis.* 2009;15:1709-1716.

Cone-rod dystrophy and amelogenesis imperfecta

Autosomal recessive (MIM217080)

In an, extensive family from the Gaza strip 29 persons had a combination of cone-rod dystrophy of the retina and amelogenesis imperfecta. There was at least 1 instance of pseudodominant inheritance. All affected members suffered from photophobia and nystagmus, starting in the first two years of life, and achromatopsia. There was no night blindness. In all affected members, the teeth were abnormally shaped and discolored as soon as they erupted.

Epidemiology:

The syndrome has been reported a single kindred in **the Gaza strip**.

Molecular genetics:

Unknown

References:

Jalili IK, Smith NJD. A progressive cone-rod dystrophy and amelogenesis imperfecta: a new syndrome. *J. Med Genet* 1988;25:738-740.

Congenital absence of alpha fetoprotein

Autosomal recessive (MIM 104150)

Alpha-fetoprotein is a major plasma protein in the fetus, where it is produced by the yolk sac and liver. In the adult its concentration is very low except when a tumor such as hepatoma or teratoma is present. AFP deficiency is a rare phenomenon, deficiency of AFP is compatible with human normal fetal development and further reproduction in males.

Epidemiology:

Two unrelated families from the small triangle

Molecular genetics:

Alphafetoprotein gene (chromosomal locus 4q11-q13)

The patients were homozygous for [T294fs25X].

References:

Sharony R, Zadik I, Parvari R. Congenital deficiency of alpha feto-protein. Eur J Hum Genet. 2004;12:871-874.

Congenital amegakaryotic thrombocytopenia

Autosomal recessive (MIM 604498)

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare bone marrow failure syndrome associated with thrombocytopenia and a tendency to progress to aplastic anemia. In most cases there are no physical abnormalities; the majority of cases progress to aplastic anemia

Epidemiology:

The disorder was reported in 4 families one Muslim Arab, one Druze and two Bedouin one from the North of Israel, the other from the Negev

Molecular genetics:

C MPL (chromosomal locus: 1p34)

In the Muslim Arab family the mutation was c.212+5GA, in the Druze family T460C and in one Bedouin family C76T and the other Bedouin family C127T

References:

Steinberg O, Gilad G, Dgany O, Krasnov T, Zoldan M, Laor R, Kapelushnik J, Gabriel H, Churi C, Stein J, Yaniv I, Tamary H. Congenital amegakaryocytic thrombocytopenia- 3 novel c-MPL mutations and their phenotypic correlations. *J Pediatr Hematol Oncol.* 2007; 29:822-825.

Congenital analbuminemia

Autosomal recessive (MIM 103600)

Congenital analbuminemia is a rare autosomal recessive disease in which albumin is not synthesized. Patients with this disorder generally have minimal symptoms despite complete absence of the most abundant serum protein. A family in which the proband presented with acute glomerulonephritis and was found to have underlying congenital analbuminemia was reported. Consequently, the patient's two older sisters were diagnosed with the same condition.

Epidemiology:

The disorder was reported in one Muslim Arab from Jerusalem

Molecular genetics:

Human serum albumin gene HSA (chromosomal locus: 4q11-q13)

In the Muslim Arab family the mutation c.228_229delAT (p.Val78CysfsX2) was found in homozygosity in the patients. The same mutation known as Kayseri was found in Turkish patients and of other ethnicity.

References:

Becker-Cohen R, Belostotsky R, Ben-Shalom E, Feinstein S, Rinat C, Frishberg Y. Congenital analbuminemia with acute glomerulonephritis: a diagnostic challenge. *Pediatr Nephrol.* 2008;24:403-406.

Congenital disorders of glycosylation CGD DK1

Autosomal recessive (MIM 610746)

Congenital disorders of glycosylation are a growing group of inborn errors of protein glycosylation. Cardiac involvement is frequently observed in the most common form, PMM2-CDG, especially hypertrophic cardiomyopathy.

Dilated cardiomyopathy dominates the clinical picture, without central nervous system or multisystem involvement, in CDG DK1 syndrome. The cardiac symptoms varies from discrete, mild dilation to overt heart failure with death.

Epidemiology and molecular genetics:

DOLK1 gene (chromosomal locus 9q32.11).

The disorder was reported in three families from the Galilee. The mutation in a Bedouin family in the north of Israel was [c.912G>T]. In two non related Druze families from two different villages the same founder mutation was found c. 1222C>G

References:

Kapusta L, Zucker N, Frenckel G, Medalion B, Gal TB, Birk E, Mandel H, Nasser N, Morgenstern S, Zuckermann A, Lefeber DJ, de Brouwer A, Wevers RA, Lorber A, Morava E. From discrete dilated cardiomyopathy to successful cardiac transplantation in congenital disorders of glycosylation due to dolichol kinase deficiency (DK1-CDG). *Heart Fail Rev.* 2013;18:187-96.

Lefeber DJ, Brouwer AP, Morava E, Riemersma M, Schuurs-Hoeijmakers JH, Absmanner B, Verrijp K, Akker WM, Huijben K, Steenbergen G, Reeuwijk J, Jozwiak A, Zucker N, Lorber A, Lammens M, Knopf C, Bokhoven H, Grünwald S, Lehle L, Kapusta L, Mandel H, Wevers RA. Autosomal recessive dilated cardiomyopathy due to DOLK mutations results from abnormal dystroglycan O-mannosylation. *PLoS Genet.* 2011;7:e1002427.

Congenital insensitivity to pain with anhidrosis (CIPA)

Autosomal recessive (MIM 256800)

Congenital insensitivity to pain with anhidrosis (CIPA) also known as hereditary sensory and autonomic neuropathy type IV belongs to a group of rare autosomal recessive peripheral sensory neuropathies. It comprises loss of pain sensation that leads to fractures, skin lacerations often evolving into deep wounds with complications such as osteomyelitis septic arthritis, and Charcot joints. Moderate to severe mental retardation is present and in combination with insensitivity to pain leads to self-mutilation of the tongue and fingertips with frequent autoamputations. Lack of sensitivity also evident in the cornea leading to traumatic ulcerations and neuro paralytic keratitis. Anhidrosis another prominent feature of the disorder is often associated with recurrent episodes of unexplained fever that can be fatal

Epidemiology:

The disease is relatively frequent in Israeli **Bedouins**.

Molecular genetics:

Receptor nerve growth factor gene, TrKA (chromosomal locus 1q21-q22)

The disease was linked to the TrKA in 9 out of 10 families. Two mutations in the tyrosine kinase domain of the TrKA gene were identified in the Bedouin patients: [1926 insT] in most of the Negev patients and [Pro 689 Leu] in a different Bedouin isolate in Northern Israel.

SCN9A gene (chromosomal location q23.3-q24.3).

In a bedouin kindred the patients were homozygous for ac.2687G>A (p.R896Q). A mutation that was not found in 130 random Bedouin individuals.

References:

Cox JJ, Sheynin J, Shorer Z, Reimann F, Nicholas AK, Zubovic L, Baralle M, Wraige E, Manor E, Levy J, Woods CG, Parvari R. Congenital insensitivity to pain: novel SCN9A missense and in-frame deletion mutations. *Hum Mutat.* 2010;31:E1670-1686

Shatzky S, Moses S, Levy J, Pinsk V, HersHKovitz E, Herzog L, Shorer Z, Luder A, Parvari R. Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli Bedouins: Genetic heterogeneity. Novel mutations in the TrKA/NGF receptor gene. Clinical findings and results of nerve conduction studies. *Am J Med Genet* 2000; 92:353-360.

Congenital lipoid adrenal hyperplasia

Autosomal recessive (MIM 600617)

The patients have a defect in the conversion of cholesterol to pregnenolone the first step in adrenal and gonadal steroidogenesis. The primary defect of congenital lipoid adrenal hyperplasia resides in steroidogenic acute regulatory protein (STAR). The genetic loss of steroidogenesis resulting from a mutation in STAR gene leads subsequently to a loss of steroidogenesis due to independent cellular damage from accumulated cholesterol esters in the adrenal cortex. Deficient steroidogenesis leads to salt wasting, hyponatremia, hypovolemia, hyperkalemia, acidosis and death in infancy, although patients can survive with appropriate mineralocorticoid and glucocorticoid replacement therapy. The males present with phenotypically normal female genitalia. Some of the affected infants have immediate signs of mineral corticosteroid deficiency while others may remain asymptomatic for months.

Prenatal diagnosis may be suggested in several cases because of the low levels of maternal estriol without any other finding when the external sex differs from the chromosomal sex.

Epidemiology:

The disease has been reported in several **Arab patients of Palestinian origin**. The mutation [c.201-202del CT] was not found in a sample of 100 Palestinians in Israel.

Molecular genetics:

Steroidogenic acute regulatory protein gene, STAR (chromosomal locus 8p11).

Two mutations are frequent in families of Palestinian [c.201-202del CT] and [R182L].

Other mutations that were reported: [R193X], [del C560] and [del2T563, R182L].

References

- Abdulhadi-Atwan M, Jean A, Chung WK, Meir K, Ben Neria Z, Stratigopoulos G, Oberfield SE, Fennoy I, Hirsch HJ, Bhangoo A, Ten S, Lerer I, Zangen DH. Role of a founder c.201_202delCT mutation and new phenotypic features of congenital lipoid adrenal hyperplasia in Palestinians. *J Clin Endocrinol Metab.* 2007;92:4000-4008.
- Bose HS, Sugawara T, Strauss J, Miller WL. The pathophysiology and genetics of congenital lipoid hyperplasia. *New Engl J Med* 1996; 335:1870-1878.
- Jean A, Mansukhani M, Oberfield SE, Fennoy I, Nakamoto J, Atwan M, Lerer I, Neria ZB, Zangen DH, Chung WK. Prenatal diagnosis of congenital lipoid adrenal hyperplasia (CLAH) by estriol amniotic fluid analysis and molecular genetic testing. *Prenat Diagn.* 2007;28:11-14.

Congenital thyroid hormone and glucocorticoid deficiency

Autosomal recessive (MIM 122560, 603372)

The affected children present in the first months of life because of hypoglycemia, hepatitis, convulsions. Some facial dysmorphism was noted in the affected children and agenesis of the corpus callosum was present in some children.

Growth and function of the thyroid and adrenal glands are maintained and controlled by thyrotropin (TSH) and adrenocorticotrophic hormone (ACTH), respectively. The action of these trophic hormones requires the presence of functional TSH and ACTH receptors. In a large inbred Bedouin kindred profound congenital hypothyroidism and hypoadrenocortisolism occurred alone or together in several family members belonging to different nuclear families. The high serum TSH and ACTH levels in the presence of normal or hypoplastic thyroid glands and low glucocorticoid, but not mineralocorticoid concentrations, are characteristic of resistance to TSH and ACTH.

The presence of hypothyroidism does not affect the timing, severity, and manner of clinical manifestation of hypoadrenocortisolism.

Prenatal diagnosis was suggested in several cases because of the low levels of maternal estriol.

Epidemiology:

The disease has been reported in 11 children from 2 villages in the **Galilee**.

Molecular genetics:

Thyrotropin receptor TSHR (chromosomal locus 14q31).

A novel point mutation was identified in exon 10 of the TSHR that replaces the normal cytosine in nucleotide 2024 with a thymidine. As a result the normal arginine in codon 609 (CGA) is replaced with a stop codon (TGA). This mutation produces a truncated TSHR lacking the third intracellular and extracellular loops, the sixth and seventh transmembrane segments, and the intracytoplasmic tail.

References:

Mandel H, Berant M, Gotfried E, Hochberg Z. Autosomal recessive hypothalamic corticotropin deficiency: a new entity and its metabolic consequences (abstract) *Am J Hum Genet* 1990;47 A66.

Tiosano D, Pannain S, Vassart G, Parma J, Gershoni-Baruch R, Mandel H, Lotan R, Zaharan Y, Pery M, Weiss RE, Refetoff S, Hochberg Z. The hypothyroidism in an inbred kindred with congenital thyroid hormone and glucocorticoid deficiency is due to a mutation producing a truncated thyrotropin receptor. *Thyroid* 1999;9:887-894.

Congenital chloride diarrhea (CLD)

Autosomal recessive (OMIM 214700)

The diarrhea begins in utero leading to polyhydramnios and prematurity. Newborn babies have abdominal distention and they do not pass meconium. Continuous water losses and electrolytes lead to dehydration and death. The diagnosis may be verified by measuring fetal chloride concentrations (higher than 90 mmol/l). Effective therapy includes daily and lifetime administration of NaCl, KCl and water allowing for normal growth and development

Epidemiology

A family was reported in a muslim Arab family and a Palestinian family living in Germany

Molecular genetics

Electroneutral intestinal Cl-/HCO₃ exchanger, SLC26A3 gene (chromosomal locus 7q31.1)

A Palestinian family living in Germany was reported and the patients were homozygous for [Q436X].

In the family from Israel the patient was homozygous for p.G187X (Shalev S), a mutation that was previously reported in Bedouin families from Kuwait.

References

Hoglund P, Sormaala M, Haila S, Socha J, Rajaram U, Scheurlen W, Sinaasappel M, de Jonge H, Holmberg C, Yoshikawa H, Kere J. Identification of seven new mutations including the first two genomic rearrangements in SLC26A3 mutated in congenital chloride diarrhea. *Hum Mutat* 2001;18:233-242

Congenital myopathy

Autosomal recessive (OMIM 180901)

In a large family, the disease was characterized by variable severity, progressive course in 3 of 4 patients, myopathic face without ophthalmoplegia and proximal muscle weakness. Absence of cores was noted in all patients.

Early onset of muscle weakness and absence of degeneration/regeneration on muscle biopsies was noted in all the patients. Furthermore, histopathological studies revealed fiber-size variation and internally-displaced nuclei

Molecular genetics

RYR1 gene (chromosomal locus 19q13.2)

All the patients were homozygous for c.9047A>G (p.Y3016C)

References

Attali R, Aharoni S, Treves S, Rokach O, Cohen MB, Fellig Y, Straussberg R, Dor T, Daana M, Mitrani-Rosenbaum S, Nevo Y. Variable Myopathic Presentation in a Single Family with Novel Skeletal RYR1 Mutation. PLOS ONE, 2013

Cutis laxa, autosomal recessive type II

Autosomal recessive (MIM 219200)

The syndrome includes facial dysmorphism (enlarged anterior fontanelles, downward slant of palpebral fissures, prominent root of the nose), a connective tissue disorder (inguinal hernia, hip dislocation, high myopia), and neurologic impairment. Early developmental delay was followed by onset of generalized seizures by the end of the first decade and a subsequent neurodegenerative course. An unusual cobblestone-like cortical malformation over the frontal and parietal regions is observed in most of the patients. Cerebellar abnormalities, including Dandy-Walker malformation, are observed in some patients. The syndrome is also reported in the literature as the wrinkly skin syndrome.

Epidemiology and molecular genetics:

ATP6VOA2 gene (chromosomal locus 12q24.3).

The mutation in a Bedouin family in the center of Israel was [c.2375C>G]

PYCR1 gene (chromosomal locus 17q25)

The disease has been reported in two Palestinian families; the mutations were [p.G206W] in one family and [c.617_633+6del] in the other.

References:

- Reversade B, Escande-Beillard N, Dimopoulou A, Fischer B, Chng SC, Li Y, Shboul M, Tham PY, Kayserili H, Al-Gazali L, Shahwan M, Brancati F, Lee H, O'Connor BD, Schmidt-von Kegler M, Merriman B, Nelson SF, Masri A, Alkazaleh F, Guerra D, Ferrari P, Nanda A, Rajab A, Markie D, Gray M, Nelson J, Grix A, Sommer A, Savarirayan R, Janecke AR, Steichen E, Sillence D, Hausser I, Budde B, Nürnberg G, Nürnberg P, Seemann P, Kunkel D, Zambruno G, Dallapiccola B, Schuelke M, Robertson S, Hamamy H, Wollnik B, Van Maldergem L, Mundlos S, Kornak U. Mutations in PYCR1 cause cutis laxa with progeroid features. *Nat Genet.* 2009; 41:1016-1021.
- Van Maldergem L, Yuksel-Apak M, Kayserili H, Seemanova E, Giurgea S, Basel-Vanagaite L, Leao-Teles E, Vigneron J, Foulon M, Grealley M, Jaeken J, Mundlos S, Dobyns WB. Cobblestone-like brain dysgenesis and altered glycosylation in congenital cutis laxa, Debre type. *Neurology.* 2008 71:1602-1608. Epub 2008 Aug 20
- Zlotogora J. Wrinkly skin syndrome and the syndrome of cutis laxa with growth and developmental delay represent the same disorder. *Am J Med Genet.* 1999;16;85:194.

Cystic fibrosis

Autosomal recessive (MIM 219700)

Cystic fibrosis was considered to be rare among non Jews in Israel but awareness and better diagnosis suggest a higher frequency of the disease in all the ethnic subgroups. In a group of 42 unrelated non Jewish patients in Israel mutations were characterized in 78 alleles: [Δ F508] 20 alleles, [N1303K] 18 alleles, [31201Kbdel8.6Kb] 11 alleles, [W1282X] 9 alleles, [G85E] 7 alleles, [2183AA>G] 4 alleles, [R75X], [4010del TATT], [del2] each in two alleles and the mutations [S549R (T>G)], [S549R (C>A)], [G542X] each in one allele. The first 4 of the mutations are found in most of the subgroups of the non Jewish population and account for 64% of the alleles.

- [31201Kbdel8.6Kb] was first described among Palestinian Arab and is relatively frequent in this population. Analysis of intragenic and flanking marker indicates that this may be an ancient mutation and indeed it was found in Muslim Arabs, Christians, Armenians and Druze.
- [N1303K] is frequent in a **village on the Mediterranean coast** and the carrier frequency was estimated by a screening of the population to be 2.7%.
- In a **village near Jerusalem** Two mutations [G85E] and [Δ F508] account for all the alleles in the CF patients from the village. Between 1975 and 1984, the incidence of cystic fibrosis in the village was estimated to be 1:72 live birth. A screening for the mutations among students from the village demonstrated that the carrier frequency for is 7.7% [G85E], 0.4% for [Δ F508]. The 5T allele is also frequent in the village (13% in the student survey) and leads to a variable phenotype and atypical clinical picture among compound heterozygotes. The 5T allele is responsible for a significant proportion of the male infertility in the village.

References:

- Chiba-Falek O, Nissim-Rafinia M, Amargan Z, Genem A, Moran I, Kerem E, Kerem B. Screening of CFTR mutations in an isolated population: identification of carriers and patients. *Eur J Hum Genet* 1998; 6:181-184.
- Laufer-Cahana A, Lerer I, Sagi M, Rachmilewitz-Minei T, Zamir H, Rivlin JR, Augarten A, Abeliovich D. Cystic fibrosis in Israeli Arab patients. *Hum Mut. Mutations in Brief* # 1999 Online.
- Lerer I, Laufer-Cahana A, Rivlin JR, Augarten A, Abeliovich D. A large deletion mutation in the CFTR gene (3120+1Kbdel8.6Kb): a founder mutation in the Palestinian Arabs. *Hum Mut Mutations in Brief* # 231 1999 Online.

Cystinuria

Autosomal recessive (MIM 220100)

The disease occurs equally in both sexes but the symptoms are usually more severe in males. The age of apparition of the first symptoms is variable. The principal clinical manifestation is renal colic due to urinary calculi; it may be associated with urinary tract obstruction, infections and later eventually loss of renal function. The stones may be cystine or uric acid. Cystinuria is a disorder of amino acid transport affecting the epithelial cells of the renal tubules and gastrointestinal tract. The cyanide-nitroprusside test may be used as a screening for the disease and the diagnosis is confirmed by quantitative examination of amino acids in urine.

Epidemiology:

The disease is common worldwide (1:15,000) and has been diagnosed in several Arab patients in Israel

Molecular genetics:

The disease is genetically heterogeneous and two genes have been reported in which mutations lead to the disorder.

SLC3A1 (chromosomal locus 2p21) (MIM 220100)

In a **Druze family** a nonsense mutation was characterized [SLC3A1, C→T 808]; the same mutation was also found in several Ashkenazi Jewish families. In a Moslem Arab family from in the **Galilee** a splicing mutation [SLC3A1, 891+4A→G] was found.

References:

Pras E, Golomb E, Drake C, Aksentijevich I, Katz G, Kastner DL. A splicing mutation (891+4A→G) in SLC3A1 leads to exon 4 splicing skipping and causes cystinuria in a Moslem Arab family. Hum Mut 1998;1:S28-30.

Pras E, Raben N, Golomb E, Arber N, Aksentijevich I, Shapiro JM et al. Mutations in the SLC3A1 transporter gene in cystinuria. Am J Hum Genet 1995;56:1297-1303.

Cystinuria+ syndrome

Autosomal recessive

In seven patients from a **Negev** Bedouin tribe, a unique syndrome, consisting of cystinuria, neonatal seizures, hypotonia, severe somatic and developmental delay, facial dysmorphism, and lactic acidemia was reported.

All the patients were born at term, with normal growth parameters. Nonetheless, all fed poorly and exhibited linear growth impairment and severe failure to thrive. At birth, all patients had generalized severe axial hypotonia and a weak cry, and five suffered from neonatal seizures. The postnatal global development was delayed, despite intact hearing, speech was incomprehensible, and moderate to severe mental retardation was evident in all the patients. Dysmorphic facies, including frontal bossing, almond-shaped eyes, long eyelashes, depressed nasal bridge, and large, posteriorly rotated ears, were noted in all patients. Renal and/or bladder cystine calculi were detected in all patients as early as 9 months of age. Reduced activity of all the respiratory chain enzymatic complexes that are encoded in the mitochondria was found in muscle biopsy specimens of the patients examined.

Molecular genetics:

The molecular basis of this disorder is a homozygous deletion of 179,311 bp on chromosome 2p16, which includes the type I cystinuria gene (SLC3A1), the protein phosphatase 2C beta gene (PP2Cbeta), an unidentified gene (KIAA0436), and several expressed sequence tags.

References:

Parvari R, Brodyansky I, Elpeleg O, Moses S, Landau D, HersHKovitz E.
A recessive contiguous gene deletion of chromosome 2p16 associated with cystinuria and a mitochondrial disease. *Am J Hum Genet* 2001; 69:869-875.

Cytochrome c oxydase deficiency

Autosomal recessive.

Several **Bedouin** children with mitochondrial myopathy due to cytochrome oxydase deficiency presented with progressive muscular weakness, failure to thrive, proximal renal tubular acidosis and lactic acidosis leading to early death. Cytochrome c oxydase was markedly reduced in skeletal muscle extracts.

Epidemiology:

The syndrome have been reported only in one family

Molecular genetics:

Unknown

References:

Kalinsky A, Funes A, Zeldin A, Pel-Or Y, Korotishevsky M, Gershoni-Baruch R et al. Autosomal recessive lethal infantile cytochrome c oxydase deficiency. Am J Child 1991; 145:661-664.

Deafness, autosomal recessive DFNB1

Autosomal recessive (MIM 220290)

Autosomal recessive deafness is frequent among non Jews in Israel and it appears that a large proportion of the patients with genetic deafness are affected because of mutations in the GJB2 gene encoding for connexin 26. The most frequent mutation being [Gdel30].

Epidemiology:

The disorder is frequent in the Mediterannean region. A particularly high incidence of the disorder has been reported in two Muslim Arab communities: **a village in the Galilee**, and a large **Bedouin tribe in the Negev**.

Molecular genetics:

Gap junction protein connexin 26 Gene (chromosomal Locus 13q11-q12).

In the Muslim Arab village in the Galilee, 3 different mutations in connexin 26 [Gdel35] and [W77R] and [V37I] has been found to be responsible for profound deafness. A screening for the mutations in random individuals in the village revealed that the carrier frequency of [Gdel35] is 7.8% and is 2.4% for [W77R] and 4.2% for [V37I].

In the **Bedouin tribe** the mutation [Gdel35] was found to be responsible for the high frequency of profound congenital deafness.

References:

- Carrasquillo MM, Zlotogora J, Barges S, Chakravarti A. Two connexin 26 mutations in an inbred kindred segregating non-syndromic deafness. *Hum Mol Genet* 1997; 6:2163-2172.
- Scott DA, Kraft ML, Carmi R, Ramesh A, Elbedour K, Yairi Y, Srisailapathy CR, Rosengren SS, Markham AF, Mueller RF, Lench NJ, Van Camp G, Smith RJ, Sheffield VC. Identification of mutations in the connexin 26 gene that cause autosomal recessive nonsyndromic hearing loss. *Hum Mutat.* 1998;11:387-394.
- Scott DA, Carmi R, Elbedour K, Yosefsberg S, Stone EM, Sheffield VC. An autosomal recessive nonsyndromic hearing loss locus identified by DNA pooling using two inbred Bedouin kindreds. *Am J Hum Genet* 1996 59:385-391.
- Zlotogora J, Carrasquillo M, Barges S, Shalev SA, Hujerat Y, Chakravarti A. High incidence of deafness from three frequent connexin 26 mutations in an isolated community. *Genet Test.* 2006;10:40-43.

Deafness, autosomal recessive DFNB7/11

Autosomal recessive (MIM 220290)

Molecular genetics and Epidemiology:

transmembrane cochlear-expressed gene 1 (TMC1), (chromosomal Locus 9q13-q21). A particularly high incidence of the disorder has been reported a large **Negev** Bedouin tribe.

References:

Scott DA, Carmi R, Elbedour K, Yosefsberg S, Stone EM, Sheffield VC. An autosomal recessive nonsyndromic-hearing-loss locus identified by DNA pooling using two inbred Bedouin kindreds. *Am J Hum Genet* 1996; 59:385-391

Scott DA, Greinwald JH Jr, Marietta JR, Drury S, Swiderski RE, Vinas A, DeAngelis MM, Carmi R, Ramesh A, Kraft ML, Elbedour K, Skworak AB, Friedman RA, Srikumari Srisailapathy CR, Verhoeven K, Van Gamp G, Lovett M, Deininger PL, Batzer MA, Morton CC, Keats BJ, Smith RJ, Sheffield VC. Identification and mutation analysis of a cochlear-expressed, zinc finger protein gene at the DFNB7/11 and dn hearing-loss loci on human chromosome 9q and mouse chromosome 19. *Gene* 1998; J30;215:461-469

Deafness, autosomal recessive DFNB 8 and DFNB10

Autosomal recessive (MIM 605316)

The gene is a transmembrane serine protease (TMPRSS3) and it was found to be mutated in the families used to describe both the DFNB10 and DFNB8 loci. In a large Palestinian family segregating an autosomal recessive form of nonsyndromic deafness the defective gene, DFNB10, was located in a 12-cM region near the telomere of chromosome 21. An 8-bp deletion and insertion of 18 monomeric (approximately 68-bp) beta-satellite repeat units was found in homozygosity in the patients.

References:

Bonne-Tamir B, DeStefano AL, Briggs CE., Adair R., Franklyn B, Weiss S, Korostishevsky M, Frydman M, Baldwin CT, Farrer L.A. Linkage of congenital recessive deafness (gene DFNB10) to chromosome 21q22.3. *Am. J. Hum. Genet.* 1996; 58: 1254-1259.

Scott HS, Kudoh J, Wattenhofer M, Shibuya K, Berry A, Chrast R, Guipponi M, Wang J, Kawasaki K, Asakawa S, Minoshima S, Younus F, Mehdi SQ, Radhakrishna U, Papasavvas MP, Gehrig C, Rossier C, Korostishevsky M, Gal A, Shimizu N, Bonne-Tamir B, Antonarakis SE. Insertion of beta-satellite repeats identifies a transmembrane protease causing both congenital and childhood onset autosomal recessive deafness. *Nat Genet* 2001;27:59-63.

Deafness, autosomal recessive.DFNB9

Autosomal recessive (MIM 603681)

Molecular genetics and Epidemiology:

gene encoding otoferlin (OTOF) (chromosomal Locus 2p23-p22).

The disorder was reported in a Druze family and the patients were homozygous for [IVS5+1G>A].

References:

Adato A, Raskin L, Petit C, Bonne-Tamir B. Deafness heterogeneity in a Druze isolate from the Middle East: novel OTOF and PDS mutations, low prevalence of GJB2 35delG mutation and indication for a new DFNB locus. Eur J Hum Genet. 2000;8:437-442.

Deafness, autosomal recessive DFNB22

Autosomal recessive (MIM 607039)

Epidemiology

The disorder was described in one Palestinian Arab family

Molecular genetics

otoanchorin gene OTOA (chromosomal locus 16p12.2)

The patients were homozygous for [IVS12+2T>C]

References

Zwaenepoel I, Mustapha M, Leibovici M, Verpy E, Goodyear R, Liu XZ, Nouaille S, Nance WE, Kanaan M, Avraham KB, Tekaiia F, Loiselet J, Lathrop M, Richardson G, Petit C. Otoanchorin, an inner ear protein restricted to the interface between the apical surface of sensory epithelia and their overlying acellular gels, is defective in autosomal recessive deafness DFNB22. *Proc Natl Acad Sci U S A.* 2002;99:6240-6245.

Deafness, mitochondrial

Mitochondrial inheritance (MIM 221745)

A very large **Muslim Arab kindred** was described in which several individuals were affected with profound sensorineural deafness maternally inherited. The disease is caused by a nucleotide 1555 A to G substitution in the mitochondrial genome. The carriers of the mutation were either with normal hearing or profound deafness demonstrating that another factor is necessary in addition the mutation order to develop deafness. It seems that the inheritance of the factors determining the penetrance is multifactorial. A mutation A10S in *TRMU* was demonstrated to be a variant frequent in the general population but found in higher frequency among deaf individuals from the kindred in some in homozygosity.

Epidemiology:

The syndrome has been reported in a single large **Muslim Arab kindred from the center** of Israel.

References:

Prezant TR, Agopian JV, Bohlman C, Bu X, Oztas S, Qiu W-Q et al.. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non syndromic deafness. *Nature Genet* 1993;4:289-293.

Deafness, autosomal recessive.PDS gene

Autosomal recessive (MIM 274600)

Molecular genetics and Epidemiology:

The locus DNFB4 was mapped to 7q31 in a Druze family in Israel as isolated congenital deafness and later the family was diagnosed as Pendred syndrome.

Epidemiology and molecular genetics:

PDS putative sulphate transporter gene SLC26A4 gene (chromosome 7q31)

The mutation T193I was found in homozygosity in the Druze family.

References:

Adato A, Raskin L, Petit C, Bonne-Tamir B. Deafness heterogeneity in a Druze isolate from the Middle East: novel OTOF and PDS mutations, low prevalence of GJB2 35delG mutation and indication for a new DFNB locus. Eur J Hum Genet. 2000;8:437-442.

Desmosterolosis

Autosomal recessive (MIM 602398)

The syndrome was reported in very few patients .the most important features include severe failure to thrive, microcephaly spasticity with various degree of contractures of hands. Most had convulsions. Brain MRI demonstrate partial or complete agenesis of corpus callosum

Molecular genetics and Epidemiology:

The syndrome was reported in several families from a Bedouin tribe from the Negev. All the patients were homozygous for c.307C>T (R103C).

References:

Zolotushko J, Flusser H, Markus B, Shelef I, Langer Y, Heverin M, Björkhem I, Sivan S, Birk OS. The desmosterolosis phenotype: spasticity, microcephaly and micrognathia with agenesis of corpus callosum and loss of white matter. *Eur J Hum Genet.* 2011;19:942-946.74.

Clinical anophthalmia, dextrocardia and skeletal anomalies

Autosomal recessive (MIM 221950)

In presumably unrelated patients born in each case of consanguineous Arab parents, a syndrome was described including dextrocardia associated with an unusual facial appearance (sloping forehead, prominent nose, large pinnae, and micrognathia), microphthalmia or clinical anophthalmia, and normal growth. Both patients had an unusual 'folding' of the plantar aspect of the foot. One patient also had vertebral fusion defects and supernumerary ribs while the other patient had cleft palate, mental retardation, and choreoathetosis .

Epidemiology:

The syndrome has been reported in two families.

Molecular genetics:

Unknown

References:

- Aughton DJ. New syndrome? Clinical anophthalmia, dextrocardia, and skeletal anomalies in an infant born to consanguineous parents. *Am J Med Genet* 1990; 37: 178-181.
- Nachlieli T, Gershoni-Baruch R. Dextrocardia, microphthalmia, cleft palate, choreoathetosis, and mental retardation in an infant born to consanguineous parents. *Am. J Med Genet* 1992;42:458-460.

Diabetes insipidus, nephrogenic

Autosomal recessive (MIM 125800)

Nephrogenic diabetes insipidus (NDI) is characterized by inability to concentrate the urine, which results in polyuria (excessive urine production) and polydipsia (excessive thirst). Affected infants usually have poor feeding and failure to thrive, and have the rapid onset of severe dehydration with an illness, hot environment, or the withholding of water. Short stature and secondary dilatation of the ureters and bladder from the high urine volume is common in untreated patients. Treatment with a very low salt diet and thiazide diuretics can reduce urine volume by up to 50%.

The clinical diagnosis of NDI relies upon demonstration of subnormal ability to concentrate the urine despite the presence of the antidiuretic hormone, pituitary-derived arginine vasopressin (AVP).

Molecular genetics and Epidemiology:

AQP2 gene (chromosomal locus 12q13).

A large cluster of patients of Bedouin origin in the **Lower-Galilee** has been reported where the mutation [G298T] was found in homozygosity.

In a consanguineous **Palestinian** family nephrogenic diabetes insipidus was due to a 1-bp deletion in the AQP2 gene; deletion of cytosine-369 (codon 123) resulted in frameshift and generation of a sequence of 8 missense amino acids followed by premature termination after amino acid position 131.

References:

- Hochberg Z, Van Lieburg A, Even L, Brenner B, Lanir N, Van Oost BA, Knoers NV
Autosomal recessive nephrogenic diabetes insipidus caused by an aquaporin-2 mutation.
J Clin Endocrinol Metab 1997;82:686-689.
- Van Lieburg AF, Verdijk MAJ, Knoers VVAM, van Essen AJ, Proesmans W, Mallmann R, Monnens LAH, van Oost BA, van Os CH, Deen PMT. Patients with autosomal nephrogenic diabetes insipidus homozygous for mutations in the aquaporin 2 water-channel gene. Am J Hum Genet 1994;55:648-652.

Diabetes insipidus, neurohypophyseal

Autosomal dominant (MIM 125700).

Familial neuro hypophyseal diabetes insipidus (FNDI) is usually an autosomal dominant disorder leading to aberrant pre prohormone processing and gradual destruction of AVP secreting cells. Patients typically present between 1-6 years of age with polyuria and polydipsia. In the one of the two Palestinian families the onset was in the neonatal period.

Epidemiology:

The syndrome has been reported in two Palestinian families with an apparent recessive inheritance. One was living in the USA the other in Jerusalem.

Molecular genetics:

Arginine vasopressin (AVP) gene (chromosomal locus 20p13).

All the patients were homozygous for the same mutation P26L with a same haplotype suggesting a founder mutation

References:

Abu-Libdeh A, Levy-Khademi F, Abdulhadi-Atwan M, Bosin E, Korner M, White P, Zangen D. Autosomal recessive familial neurohypophyseal diabetes insipidus - onset in early infancy. *Eur J Endocrinol.* 2010;162:221-226.

Willcutts MD, Felner E, White PC. Autosomal recessive familial neurohypophyseal diabetes insipidus with continued secretion of mutant weakly active vasopressin. *Hum Mol Genet* 1999;8:1303-1307.

Diabetes mellitus

In a large **Bedouin Arab family** type 1 diabetes appeared in three generations. The inheritance was compatible with a monogenic trait and dominant inheritance. Linkage analysis allow mapping to the long arm of chromosome 10 (10q25; nonparametric linkage = 4.99; $P = 0.00004$). All affected relatives carry one or two high-risk HLA-DR3 haplotypes that are rarely found in other family members. One chromosome 10 haplotype, the B haplotype, was transmitted from a heterozygous parent to 13 of 13 affected offspring compared to 10 of 23 unaffected siblings. Recombination events occurring on this haplotype place the susceptibility locus in an 8-cM interval between markers D10S1750 and D10S1773.

References:

Verge CF, Vardi P, Babu S, Bao F, Erlich HA, Bugawan T, Tiosano D, Yu L, Eisenbarth GS, Fain PR. Evidence for oligogenic inheritance of type 1 diabetes in a large Bedouin Arab family. *J Clin Invest* 1998;102:1569-1575.

Diabetes mellitus, neonatal

Autosomal recessive (MIM 606176)

Neonatal diabetes mellitus, defined as insulin-requiring hyperglycemia within the first month of life, is a rare entity, with an estimated incidence of 1 in 400,000 neonates. In about half of the neonates, diabetes is transient and resolves at a median age of 3 months and is associated with abnormalities of chromosome 6 whereas the rest have a permanent form of diabetes.

Epidemiology:

Permanent neonatal diabetes has been reported in two infants from an Arab inbred family

Molecular genetics:

Glucokinase (GCK) gene (chromosomal locus 7p15-p13).

One patient was homozygous for the mutation IVS*+2 and the other compound heterozygous IVS+2/G264S.

References:

Njolstad PR, Sagen JV, Bjorkhaug L, Odili S, Shehadeh N, Bakry D, Sarici SU, Alpay F, Molnes J, Molven A, Sovik O, Matschinsky FM Permanent neonatal diabetes caused by glucokinase deficiency: inborn error of the glucose-insulin signaling pathway. *Diabetes*. 2003;52:2854-2860.

Diaphanospondylodysostosis (DSD)

Autosomal recessive (MIM 608022)

Diaphanospondylodysostosis is a rare, lethal skeletal disorder.

The condition is classified as a dysostosis, since it is a static skeletal malformation occurring early in development (during blastogenesis). The spine is most prominently affected, with diaphanous, that is, translucent vertebrae, due to abnormal vertebral ossification and segmentation. Other skeletal defects include thoracic hypoplasia with abnormal rib structure and shape and enlarged fontanelles.

The kidneys are cystic and dysplastic, and microscopically nephroblastomatosis (embryonic nephrogenic rests) is observed.

Death usually occurs perinatally due to respiratory failure.

Molecular genetics and epidemiology:

BMPER gene (chromosomal locus 19q13.1-q13.3).

The syndrome was reported in two unrelated families from East Jerusalem. A same mutation was found in homozygosity c.310 C>T, Q104X that was not detected in 123 control samples from the same population.

References:

Ben-Neriah Z, Michaelson-Cohen R, Inbar-Feigenberg M, Nadjari M, Zeligson S, Shaag A, Zenvirt S, Elpeleg O, Levy-Lahad E. Deleterious founder mutation in the BMPER gene causes diaphanospondylodysostosis (DSD). *Am J Med Genet A*. 2011;155A:2801-2806.

Dyserythropoietic anemia type I (congenital)

Autosomal recessive (MIM 224120)

Congenital dyserythropoietic anemias (CDA) are a rare group of red blood cell disorders of unknown etiology characterized by ineffective erythropoiesis, pathognomonic cytopathology of the nucleated red blood cells in the bone marrow and secondary hemochromatosis. Type I is characterized by congenital macrocytic anemia, megaloblastic erythroid hyperplasia and the presence of nuclear chromatin bridges between erythroblasts.

The clinical picture among the Bedouin patients was variable but mostly benign, the age of diagnosis was between birth to 23 years and 6 of the 20 patients required occasional transfusions.

Epidemiology:

The disease has been reported in 7 **Bedouin families from the Negev** belonging to the same tribal group.

Molecular genetics:

Codanin-1 gene (chromosomal locus 15q15.1-15.3)

The Bedouin patients were homozygous for a R1040W mutation in the Codamin-1 gene. Another mutation 3238C>T was diagnosed in a Bedouin patient. Two mutations were characterized among Muslim Arabs [V867M] and IVS-12+5G>A.

References:

Dgany O, Avidan N, Delaunay J, Krasnov T, Shalmon L, Shalev H, Eidelitz-Markus T, Kapelushnik J, Cattani D, Pariente A, Tulliez M, Crétien A, Schischmanoff P-O, Iolascon A, Fibach E, Koren A, Rössler J, Le Merrer M, Yaniv I, Zaizov R, Ben-Asher E, Olender T, Lancet D, Beckmann JS, Tamary H. Congenital Dyserythropoietic Anemia Type I Is Caused by Mutations in Codanin-1. *Am J Hum Genet* 2002;71:1467-1474.

Tamary H, Shalev H, Luria D, Shaft D, Zoldan M et al.. Clinical features and studies of erythropoiesis in Israeli Bedouins with congenital dyserythropoietic anemia type I. *Blood* 1996;87:1763-1770.

Dysmegakaryopoiesis, mild anemia and neutropenia

Autosomal recessive

Familial thrombocytopenia is a relatively rare and heterogeneous group of clinical and genetic syndromes of unknown etiology. Four members of a Bedouin family presented with congenital thrombocytopenia of neonatal onset associated with anemia and neutropenia. There was a severe bleeding tendency, including intracranial hemorrhage in three. Bone marrow EM revealed dysmegakaryopoiesis with delayed nuclear or cytoplasmic maturation and a tendency to increased cytoplasmic membrane formation. Three of the four were successfully treated with allogenic human leukocyte antigen (HLA)-matched bone marrow transplants.

Epidemiology:

The disease has been reported in 4 individuals in a large **Bedouin kindred from the Negev**

Molecular genetics:

No data

References:

Tamary H, Yaniv I, Stein J, Dgany O, Shalev Z, Shechter T, Resnitzky P, Shaft D, Zoldan M, Kornreich L, Levy R, Cohen A, Moser RA, Kapelushnik J, Shalev H. A clinical and molecular study of a Bedouin family with dysmegakaryopoiesis, mild anemia, and neutropenia cured by bone marrow transplantation. *Eur J Haematol.* 2003;71:196-203.

Ectodermal dysplasia, anhidrotic

Autosomal recessive (MIM 129490)

The main features include decreased sweating, hypotrichosis of the scalp, sparse eyebrows and eyelashes and sparse or absent body hair. The teeth are conical and hypodontia is the rule. The nails are normal. Episodes of hyperthermia are frequent in most affected patients.

Epidemiology:

The disease has been reported in several individuals in a large **Muslim Arab kindred** and was diagnosed in **one Muslim Arab family in the Galilee**.

Molecular genetics:

EDAR ectodysplasin *DL* gene (chromosomal locus 2q11-q13)

Two Druze family the mutation was characterized Cys87Arg (exon 4) (Borochowitz Z)

References:

Montreal AW, Ferguson BM, Headon DJ, Street SL, Overbeek PA, Zonana J. Mutations in the human homologue of mouse *dl* cause autosomal recessive and dominant ectodermal dysplasia. *Nature Genet* 1999; 22:366-369.

Munoz F, Lestringant G, Sylbert V, Frydman M, Alswaini A, Frossard PM, Jorgenson R, Zonana J. Definite evidence for an autosomal recessive form of hypohydrotic ectodermal dysplasia clinically indistinguishable from the more common X-linked disorder. *Am J Hum Genet* 1997;61:94-100.

Enhanced S-cone syndrome

Autosomal recessive (MIM 268100)

Hereditary human retinal degenerative diseases usually affect the mature photoreceptor topography by reducing the number of cells through apoptosis, resulting in loss of visual function. Only one inherited retinal disease, the enhanced S-cone syndrome (ESCS), manifests a gain in function of photoreceptors.

The patients have increased sensitivity to blue light; perception of blue light is mediated by what is normally the least populous cone photoreceptor subtype, the S (short wavelength, blue) cones. People with ESCS also suffer visual loss, with night blindness occurring from early in life, varying degrees of L (long, red)- and M (middle, green)-cone vision, and retinal degeneration. The pattern of retinal dysfunction is a constant among ESCS patients, but the degree of clinically evident retinal degeneration can vary from minimal to severe. The latter condition is known as Goldmann-Favre syndrome that is characterized by a liquefied vitreous body with preretinal band-shaped structures (veil), macular changes in the form of retinoschisis or edema and pigmentary degeneration of the retina with hemeralopia and extinguished electroretinogram. Cataract is a complication.

Epidemiology:

The disease has been diagnosed among in several Palestinian Muslim Arab families from the Galilee, Jerusalem and the territories.

Molecular genetics:

NR2E3 gene (chromosomal locus 15q23)

A same mutation [119-2A>C] was found in all the Palestinian Arabs

References:

Bandach D, Merin S, Ashlab M, Banin E, Sharon D. The spectrum of retinal diseases caused by NR2E3 mutations in Israeli and Palestinian patients. Arch Ophthalmol 2009;127: 297-302.

Enteropathy, protein-losing

Autosomal recessive (MIM 226300)

The disease has been reported in 8 children from 2 sibships from a Christian Arab kindred living in **the Galilee**. The affected children presented with edema, growth retardation, diarrhea, abdominal pain and clubbing. There was a great variation in the severity of the disease between the affected children from a mild to very severe. In four children death occurred in a picture of hepatic failure with ascites. At autopsy in two hepatic vein thrombosis was present which caused a Budd-Chiari syndrome.

Epidemiology:

The syndrome have been reported in a single family

Molecular genetics:

Unknown

References:

Shani M, Theodor E, Frand M, Goldman G. A family with protein losing enteropathy. *Gastroenterology* 1974;66:433-445.

Epidermolysis bullosa simplex

Autosomal dominant or recessive (MIM 131750,131760, 131900)

EB represents a group of different skin disorders in which the most severe are present at birth with bullous lesions and early death. EB is classified according to the level of dermal epidermal separation at the basal membrane zone. EB simplex results from separation of the skin above the basal membrane.

Three clinical subtypes have been classically described: palm and palms (Weber-Cockayne), general distribution of blisters (Koebner) and more extensive and severe blistering affecting often mucosae and nails (Dowling Malera).

Among the less severe forms most have been described with a dominant inheritance, however, several cases with recessive inheritance were reported in rule with a more severe clinical picture.

Epidemiology:

Epidermolysis bullosa simplex is relatively frequent in all populations and has been diagnosed in several non-Jewish families in Israel.

Molecular genetics:

Epidermolysis bullosa simplex is caused by mutations in genes encoding for keratin 5 (K5) or 14 (K14).

Muslim Arab patients homozygotes for a recessive mutation in K14 [W305X] or [R134C].

Muslim Arabs patients with a dominant mutation in KRT14 [R125C] or in KRT 5 [G406D] and [G476D].

Druze patients with a dominant mutation in K14 [Y415C] and [R125H] or in KRT5 [I467K].

References:

Ciubotaru D, Bergman R, Baty D, Indelman M, Pfendner E, Petronius D, Moualem H, Kanaan M, Ben Amitai D, McLean WH, Uitto J, Sprecher E. Epidermolysis bullosa simplex in Israel: clinical and genetic features. Arch Dermatol. 2003;139:498-505.

Abu Sa'd J, Indelman M, Pfendner E, Falik-Zaccai TC, Mizrachi-Koren M, Shalev S, Amitai DB, Raas-Rothschild A, Adir-Shani A, Borochowitz ZU, Gershoni-Baruch R, Khayat M, Landau D, Richard G, Bergman R, Uitto J, Kanaan M, Sprecher E. Molecular Epidemiology of Hereditary Epidermolysis Bullosa in a Middle Eastern Population. J Invest Dermatol. 2006;126:777-781.

Epidermolysis bullosa, generalized atrophic benign

Autosomal recessive (MIM 113811)

EB represents a group of different skin disorders; generalized atrophic benign epidermolysis bullosa is a nonlethal form of junctional EB with an autosomal recessive inheritance. There is generalized cutaneous blister formation at sites of trauma, atrophic alopecia affecting scalp, eyelash and eyebrow, dystrophic nail changes, and tooth abnormalities.

Epidemiology:

Generalized atrophic benign epidermolysis bullosa has been diagnosed in **several Muslim Arab families**.

Molecular genetics:

COL17A1 (chromosomal locus 10q24.3)

In a family, from Lod (founder was from Hebron) the disease was caused by a homozygous donor splice site mutation, [IVS51+1G>A].

Other recessive mutations [4767delA], [2226insTGGA], [737insA], [G923R], [W796X], [6341 delG], [6339G].

References:

Whitlock NV, Sher C, Gold I, Libman V, Reish O. A founder COL17A1 splice site mutation leading to generalized atrophic benign epidermolysis bullosa in an extended inbred Palestinian family from Israel. *Genet Med.* 2003;5:435-439.

Abu Sa'd J, Indelman M, Pfendner E, Falik-Zaccai TC, Mizrachi-Koren M, Shalev S, Amitai DB, Raas-Rothschild A, Adir-Shani A, Borochowitz ZU, Gershoni-Baruch R, Khayat M, Landau D, Richard G, Bergman R, Uitto J, Kanaan M, Sprecher E. Molecular Epidemiology of Hereditary Epidermolysis Bullosa in a Middle Eastern Population. *J Invest Dermatol.* 2006;126:777-781.

Epidermolysis bullosa lethalis

Autosomal recessive (MIM 226700)

EB represents a group of different skin disorders in which the most severe are present at birth with bullous lesions and early death.

Junctional epidermolysis bullosa Herlitz type is characterized by the formation of widespread blisters and erosions of the skin following minor trauma. The hand and feet are relatively spared. Loss of serum, protein and electrolytes and dermal sepsis seem to be responsible for early neonatal or childhood death. The disease results from mutations in the J2 and J3 chains of the laminin 5 protein.

In one family the association of epidermolysis bullosa and diaphragmatic hernia was reported in two sibs who died few hours after birth.

A distinct syndrome was described with epidermolysis bullosa and pyloric atresia (MIM 226730).

Epidemiology:

Junctional epidermolysis bullosa Herlitz type has been diagnosed in several Arab families of Christian and Muslim Arab origin. The disease appears to be one of the most frequent monogenic causes of infant mortality among Arabs (1/10,000 live births).

Molecular genetics:

Epidermolysis bullosa lethalis is caused by mutations in any 1 of the 3 polypeptides of laminin-5:

alpha-3 (LAMA3) K1594N, 2942delA, 860_861insT

beta-3 (LAMB3) Q1083X, 2528delA, 1296 insA, R792X,

gamma-2 (LAMC2) 368_373delinsACCAC

In two families with JEB-nonHerlitz type, the patients were homozygous for COL17A1 4144del4 and 3766+1G>A

References:

Duduin A, Thalji A. Diaphragmatic hernia and epidermolysis bullosa in two sibs. Am J Med Genet 1991;39:498-499

Abu Sa'd J, Indelman M, Pfendner E, Falik-Zaccai TC, Mizrachi-Koren M, Shalev S, Amitai DB, Raas-Rothschild A, Adir-Shani A, Borochowitz ZU, Gershoni-Baruch R, Khayat M, Landau D, Richard G, Bergman R, Uitto J, Kanaan M, Sprecher E. Molecular Epidemiology of Hereditary Epidermolysis Bullosa in a Middle Eastern Population. J Invest Dermatol. 2006;126:777-781

Epidermolysis bullosa, pyloric atresia and aplasia cutis congenita (Carmi syndrome)

Autosomal recessive (MIM 226730)

The simultaneous appearance of epidermolysis bullosa and pyloric atresia is known as a rare autosomal recessive syndrome. The disease is severe and most of the patients die soon after birth. In many of the patients large areas of congenital absence of skin are noted. The association with aplasia cutis congenita does not seem coincidental and it is probably a component of the syndrome. A patho-physiologic hypothesis was formulated to explain the association. The basic pathology involves at least 2 components: the integrity of the basement membrane and hemidesmosomes and the control of the normal process of fibrosis occurring in the course of wound healing. The sequence of events is initiated by the separation of the epidermis or the intestinal mucosal layer along with the disruption of hemidesmosomes. Then inflammatory response takes place with massive fibrosis penetrating the deep layer and causing the destruction of the skin and obstruction of the intestinal lumina.

Epidemiology:

The syndrome has been reported in several patients from a large **Bedouin kindred from the Negev**.

Molecular genetics:

The disorder can be caused by mutations in the integrin-beta-4 gene (ITGB4) and the integrin-alpha-6 gene (ITGA6).

In the bedouin Kindred the patients are homozygous for a deletion of a 2279bp fragment in the ITGB4 gene. In a muslim family a E39R was diagnosed

References:

- Birnbaum RY, Landau D, Elbedour K, Ofir R, Birk OS, Carmi R. Deletion of the first pair of fibronectin type III repeats of the integrin beta-4 gene is associated with epidermolysis bullosa, pyloric atresia and aplasia cutis congenita in the original Carmi syndrome patients. *Am J Med Genet A*. 2008;146A:1063-1066.
- Carmi R, Sofer S, Karplus M, Ben-Yakar Y, Mahler D, Zirkin H, Bar-Ziv J. Aplasia cutis congenita in two sibs discordant for pyloric atresia. *Am J Med Genet*. 1982;11:319-328

Epilepsy and mental retardation limited to females (EFMR)

X linked (MIM 300088)

Epilepsy and Mental Retardation limited to Females (EFMR) was described in a single family characterized by onset of convulsions in infancy in previously normal girls who subsequently showed developmental regression, with mild to profound intellectual disability (ID). The disorder has an extraordinary pattern of inheritance, regarded as X-linked dominant with male sparing, where females are affected and males transmit the disorder; males have been regarded as phenotypically normal.

In a new report including a Arab Israeli family twenty-seven affected females had a mean seizure onset of 14 months typically presenting with convulsions. All had convulsive attacks at some stage, associated with fever in most. Multiple seizure types occurred including tonic-clonic, tonic, partial, absence, atonic and myoclonic. Seizures ceased at mean 12 years. Developmental progress varied from normal, to always delayed to normal followed by regression. Intellect ranged from normal to severe intellectual disability, with 67% of females having ID or being of borderline intellect. Autistic, obsessive and aggressive features were prominent. EEGs showed generalized and focal epileptiform abnormalities. Five obligate male carriers had obsessional tendencies.

Molecular genetics:

PCDH19 (chromosomal locus Xq22)

In the Arab Israeli the mutation [2012C>G] was characterised in all the patients.

References:

Dibbens LM, Tarpey PS, Hynes K, Bayly MA, Scheffer IE, Smith R, Bomar J, Sutton E, Vandeleur L, Shoubbridge C, Edkins S, Turner SJ, Stevens C, O'Meara S, Tofts C, Barthorpe S, Buck G, Cole J, Halliday K, Jones D, Lee R, Madison M, Mironenko T, Varian J, West S, Widaa S, Wray P, Teague J, Dicks E, Butler A, Menzies A, Jenkinson A, Shepherd R, Gusella JF, Afawi Z, Mazarib A, Neufeld MY, Kivity S, Lev D, Lerman-Sagie T, Korczyn AD, Derry CP, Sutherland GR, Friend K, Shaw M, Corbett M, Kim HG, Geschwind DH, Thomas P, Haan E, Ryan S, McKee S, Berkovic SF, Futreal PA, Stratton MR, Mulley JC, Géczy J. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nat Genet* 2008;40:776-781. Scheffer IE, Turner SJ, Dibbens LM, Bayly MA, Friend K, Hodgson B, Burrows L, Shaw M, Wei C, Ullmann R, Ropers HH, Szepietowski P, Haan E, Mazarib A, Afawi Z, Neufeld MY, Andrews PI, Wallace G, Kivity S, Lev D, Lerman-Sagie T, Derry CP, Korczyn AD, Gecz J, Mulley JC, Berkovic SF. Epilepsy and mental retardation limited to females: an under-recognized disorder. *Brain*. 2008;131:918-927.

Factor V Leiden thrombophilia

Factor V Leiden thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC), and an increased risk of venous thromboembolism. The term "factor V Leiden" refers to the specific G to A substitution at nucleotide 1691 in the gene for factor V that predicts a single amino acid replacement (Arg506Gln) at one of three APC cleavage sites in the factor Va molecule. Factor V Leiden is inactivated at an approximately 10-fold slower rate than normal factor V and persists longer in the circulation, resulting in increased thrombin generation and a mild hypercoagulable state reflected by elevated levels of prothrombin fragment F1+2 and other activated coagulation markers. Individuals heterozygous for the factor V Leiden mutation have a slightly increased risk for venous thrombosis, and homozygous individuals have a much greater thrombotic risk.

Epidemiology.

The disorder is frequent among Arabs in Israel and Jordan. Among 70 Israeli Arabs the allele frequency was 0.134 while in Jordan in a total of 400 subjects the allele frequency was 0.07.

References:

- Awidi A, Shannak M, Bseiso A, Kailani MA, Kailani MA, Omar N, Anshasi B, Sakarneh N. High prevalence of factor V Leiden in healthy Jordanian Arabs. *Thromb Haemost* 1999; 81:582-584.
- Rosen E, Renbaum P, Heyd J, Levy-Lahad E. High frequency of factor V Leiden in a population of Israeli Arabs. *Thromb Haemost* 1999; 82:1768.

Factor VII deficiency

Autosomal recessive (MIM 227500)

The patients have in rule mild bleeding symptoms but a severe disease was reported in several families.

Molecular genetics and epidemiology:

Factor VII gene (chromosomal locus 13q34)

In four unrelated Druze patients the same mutation [Cys310Phe] was characterized. Other mutations were Phe24 del (Christians), IV52+1G>C each in one patient and causing a severe disease in homozygosity. The mutation G180R was found in one Bedouin family from the Negev

References:

Fromovich-Amit Y, Zivelin A, Rosenberg N, Tamary H, Landau M, Seligsohn U. Characterization of mutations causing factor VII deficiency in 61 unrelated Israeli patients. *J Thromb Haemost.* 2004;2:1774-1781.

Factor XI deficiency (PTA)

Autosomal recessive (MIM 264900)

The affected patients present with a general mild bleeding tendency which is often diagnosed after a trauma, a dental or a surgical procedure. Some of the patients also present spontaneous bleeding like hemarthrosis or purpura.

The biochemical defect is the deficiency of factor XI coagulant activity.

Epidemiology:

Factor XI deficiency has been described in two families

Molecular genetics:

Factor XI, FXI (chromosomal locus 4q35)

A C to A mutation in exon 11 at nucleotide 1254 resulting in [T386N] was found in two patients (father and daughter) with severe deficiency of factor XI.

References:

Agai E, Yaniv I, David M. Factor XI deficiency in an Arab Moslem family in Israel. *Scan J Hematol* 1984; 32:327-331.

Wistenghausen B, Reischer A, Oddoux C, Ostrer H, Nardi M, Karparkin M. Severe factor XI deficiency in an Arab family associated with a novel mutation in exon 11. *Br J Hematol* 1997;99:575-577.

Factor XIII deficiency

Autosomal recessive (MIM 134570)

Factor XIII is the last enzyme generated in the blood coagulation cascade. Plasma factor XIII is composed of 2 A subunits, which have catalytic function, and 2 B subunits.. The B subunit of plasma factor XIII do not have transglutaminase activity and may serve as a carrier, since platelet factor XIII consists simply of A2 dimers. Factor XIII is activated by the cleavage of a small peptide from the A subunit by thrombin thus generating the transamidase.

The F13A1 gene maps to 6p25-p24 and is linked to the MHC region.

Homozygotes for factor XIII deficiency show umbilical stump bleeding, high frequency of fetal wastage, soft tissue hemorrhage, and intracranial hemorrhage. Males show oligospermia and small testes.

Because of the long half-life of infused factor XIII and the small amounts necessary for normal hemostasis, both replacement therapy and prophylaxis are simple, effective, and relatively inexpensive.

Epidemiology:

The disorder has been reported in several unrelated **families**. The disorder is frequent in a **village in the center of Israel** (Frydman M)

Molecular genetics:

The gene for the A1 subunit of FXIII, F13A1 (chromosomal locus 6p25).

The patients reported in the literature were homozygotes for a same mutation in the gene for the A subunit of FXIII [Leu660 Pro].

In a sample of 300 Arabs the mutation was detected in two and the estimated mutation frequency is 0.0033.

References:

Inbal A, Yee VC, Kornbrot N, Zivelin A, Brenner B, Seligsohn U. Factor XIII deficiency due to a Leu660Pro mutation in the factor XIII subunit a gene in three unrelated Palestinian Arab families. *Thromb Haemost* 1997;77:1062-1067.

Familial Mediterranean Fever

Autosomal recessive (MIM 249100)

The disease is characterized by short periodic attacks of fever together with painful manifestations in the abdomen, chest, joints or skin without any known causative factor. In most patients the first symptoms may appear by the age of 10 and in 90% of the patients by the age of 20. Fever is a constant feature but is rarely the sole symptom, usually it is preceded by pain. Most attacks are of 12 to 24 hours duration, some are longer in particular when the joints are involved. The abdominal crisis are the most common and dramatic form of the attacks and cause an acute like abdomen and often the patient are operated on in the first attacks. Classically the pains disappear after a day and are followed by diarrhea. Chest attacks are mainly caused by pleural pains. When the joints are involved generally the symptoms are mono articular mainly affecting the knee, the ankle or the hip. Most attacks present with a rapidly evolving arthritis with exquisite tenderness and immobilization of the joint. In the synovial fluid, leukocytes may be found but the fluid is sterile. There is no residual joint deficit after the attack. Involvement of the skin during an attack is in the form of erysipelas like erythema. The most important complication of the disease is the development of amyloidosis. Amyloid nephropathy is independent of the severity of the other signs of the disease and may appear at early age. The manifestations are first proteinuria and nephrotic syndrome and renal failure. Treatment with colchicine reduce the symptoms and the frequency of the periodic attacks and may prevent the development of amyloidosis.

Molecular genetics:

MEFV (chromosomal locus 16p13)

In a large sample of non-related non-Jewish patients from Israel mutations in *MEFV* were characterized:

Origin	N*	M694V	V727A	M694I	M6801I	E148Q	?
Muslim	120	15	27	3	24	7	44
Christian	6		2		2		2
Druze	16		3	2		1	10

*chromosomes

References:

Gershoni-Baruch R, Kepten I, Shinawi M, Brik R. Direct detection of common mutations in the familial Mediterranean fever gene (*MEFV*) using naturally occurring and primer mediated restriction fragment analysis. Hum Mut 1999 Mutation in brief #257 online.

Fanconi Anemia

Autosomal recessive (MIM 227650)

The most common presentation is a congenital malformation in particular a radial defect which may range from bilateral absent thumb and radii to relatively minor thumbs anomalies. Other malformations are also frequent such as cardiac, renal or other skeletal abnormalities. However, in one third of the patients no malformations are present but there are often minor anomalies such as skin pigmentation abnormalities, short stature or small head circumference.

The major problem is the marrow failure that affects all the elements resulting in anemia, thrombopenia and leukopenia

The presence of typical chromosomal breaks induced by a clastogenic agent such as di epoxybutane (DEB) is pathognomonic.

Epidemiology:

The disease has been diagnosed in several **Arab families** in Israel.

Molecular genetics:

FANCA gene

gross deletion of exons 6-31 in one family from the region of "the small triangle"
V229I, splice-site mutation IVS 42-2A>C in two families from the lower Galilee.

FANCG gene

splice-site mutation IVS4+3A>G in one family in a town in vaadi Ara

References:

Tamary H, Dgany O, Toledano H, Shalev Z, Krasnov T, Shalmon L, Schechter T, Bercovich D, Attias D, Laor R, Koren A, Yaniv I. Molecular characterization of three novel Fanconi anemia mutations in Israeli Arabs. Eur J Haematol 2004;72:330-335.

Fanconi Anemia like syndrome

Autosomal recessive

A family in which three siblings born to related parents all manifested clinical abnormalities characteristic of Fanconi anaemia (microcephaly, short stature, slow growth, beak nose, micrognathia, skin dyspigmentation and forearm and thumb dysplasia) was reported in a Palestinian family living in Saudi Arabia. The syndrome has been also characterized in several patients from a **village near Jerusalem**. In the village, all the affected presented with bilateral thumb malformations (absence, hypoplasia..) which were often asymmetric. In most of the patients the radial rays were normal. Another constant feature was microcephaly with variable degree of mental impairment from low normal intelligence to mental retardation. The affected children often presented with other malformations in particular of the cardiac, skeletal or nervous systems. The birth weight was always low for gestational age and thereafter the children developed with short stature. All the adult patients were infertile and had hypogonadism.

None of the patients presented with hematological manifestations, the chromosome were normal and there was no induced chromosome breakage excluding therefore Fanconi anemia.

Epidemiology:

The syndrome has been reported in several **Muslim Arab** families from a **single village near Jerusalem** and in a Palestinian family of unknown origin.

Molecular genetics:

Unknown

References:

- Milner RD, Khallouf KA, Gibson R, Hajianpour A, Mathew CG. A new autosomal recessive anomaly mimicking Fanconi's anaemia phenotype. Arch Dis Child 1993; 68:101-103.
- Zlotogora J, Dagan J, Ganen A, Abu-Libdeh M, Ben-Neriah Z, Cohen T. A syndrome including thumb malformations, microcephaly, short stature and hypogonadism. J Med Genet 1997;34:813-816.

Fanconi syndrome with hypophosphatemic rickets.

Autosomal recessive

A family in which two siblings with autosomal recessive proximal tubulopathy associated with severe renal phosphate wasting, hypophosphatemic rickets, and renal failure.

Epidemiology:

The syndrome has been reported in a **Muslim Arab** family.

Molecular genetics:

SLC34A1 gene (*chromosomal locus 5q35.1–q35.3*)

Sequence analysis of *SLC34A1* in both patients revealed a homozygous in-frame duplication of 21 bp (g.2061_2081dup) in exon 5, causing a duplication of seven amino acids (ILVTVLV) at positions 154 to 160 of the NaPi-IIa protein (p.I154_V160dup)

References:

Magen D, Berger L, Coady MJ, Ilivitzki A, Militianu D, Tieder M, Selig S, Lapointe JY, Zelikovic I, Skorecki K. A Loss-of-Function Mutation in NaPi-IIa and Renal Fanconi's Syndrome. *NEJM* 2010;362:1102-1109.

Focal epilepsy and intellectual disability syndrome

Autosomal recessive

A pedigree in which several individuals with focal seizures with prominent eye blinking and facial and limb jerking began at around 2 months of age and persisted throughout life. The patients described an aura with the sensation of the tongue being anaesthetized.

Convulsive seizures also occurred but were generally controlled by antiepileptic medication.

Early motor and speech development was mildly delayed in some children, and in adult life there was borderline to moderate ID associated with mild dysarthria and ataxia.

MRI showed features that we interpreted as abnormal cortical thickening, most obvious in the anteromesial frontal areas.

Epidemiology:

The syndrome has been reported in a large Muslim Arab family in the Galilee.

Molecular genetics:

TBC1D24 gene (chromosomal locus 16p13.3)

the patients were homozygous for c.751C>T (p.F251L) mutation

References:

Corbett MA, Bahlo M, Jolly L, Afawi Z, Gardner AE, Oliver KL, Tan S, Coffey A, Mulley JC, Dibbens LM, Simri W, Shalata A, Kivity S, Jackson GD, Berkovic SF, Gecz J. A Focal Epilepsy and Intellectual Disability Syndrome Is Due to a Mutation in TBC1D24. *Am J Hum Genet.* 2010;10;87:371-375.

Frank-Ter Haar Syndrome

Autosomal recessive (MIM 249420)

The patients present with megalocornea, brachycephaly, large anterior fontanelles, hypertelorism, anteverted nostrils, thoracolumbar kyphosis, prominent coccyx, short hands, flexion deformity of fingers, club feet, and cardiac involvement. FTHS patients usually die in infancy or in early childhood because of the cardiovascular anomalies, respiratory infections, or unknown causes.

Epidemiology and Molecular genetics:

SH3PXD2B gene (chromosomal locus 5q35.1)

The disease has been diagnosed in Muslim Arab family from Jerusalem. The patient was homozygous for a c.76-2A>C mutation.

References:

Iqbal Z, Cejudo-Martin P, de Brouwer A, van der Zwaag B, Ruiz-Lozano P, Scimia MC, Lindsey JD, Weinreb R, Albrecht B, Megarbane A, Alanay Y, Ben-Neriah Z, Amenduni M, Artuso R, Veltman JA, van Beusekom E, Oudakker A, Millán JL, Hennekam R, Hamel B, Courtneidge SA, van Bokhoven H. Disruption of the Podosome Adaptor Protein TKS4 (SH3PXD2B) Causes the Skeletal Dysplasia, Eye, and Cardiac Abnormalities of Frank-Ter Haar Syndrome. *Am J Hum Genet.* 2010 Feb 3. [Epub ahead of print]

Autosomal recessive (MIM 229700)

This rare inborn error of metabolism can cause life-threatening episodes of hypoglycemia. The disease present in infancy in the form of easily controllable neonatal hypoglycemia in particular during febrile illnesses associated with reduced food intake and vomiting. Slight to moderate hepatomegaly with abnormal liver functions has been observed.

Epidemiology:

The disease has been diagnosed in **Muslim Arab and Druze** families in Israel.

Molecular genetics:

Unknown

References:

Moses SW, Bashan N, Flaterstein BF, Rachmel A, Gutman A. Fructose 1-6 diphosphatase deficiency in Israel. *Isr J Med Sc* 1991;37:1-4.

Gaucher disease

Autosomal recessive (MIM 230800)

Gaucher disease type I is also known as the adult, non neuronopathic type, even though the first symptoms of the disease may first appear in infancy. Some of the patients are asymptomatic and the disease is discovered in an apparently healthy individual; while others present with a severe disease with symptoms appearing in early childhood, mainly splenomegaly, anemia thrombocytopenia and often symptoms related to the bone involvement such as pains or pathological fractures. Most of the patients present with an intermediate severity of the disease when the age of onset is at the second and third decade of life, sometimes discovered in women during a pregnancy. The severity and degree of suffering depend upon which organ is most severely involved and is variable from one individual to the other.

In the other types of Gaucher disease some neurological symptoms are present either in infancy or later in life.

Epidemiology and molecular genetics:

- Gaucher disease type I was diagnosed in several patients in a **Muslim Arabvillage in the Galilee** [N370S]
- Gaucher disease type I was diagnosed in several Bedouin from the Negev patients all had at least one allele [R48W]
- A variant of Gaucher disease has been diagnosed in several patients in **villages around Jenin and in Israel in a town of the small triangle**.
Oculomotor apraxia was the presenting symptom in all the patients. Cardiac involvement typically consisted of progressive thickening and calcification of the mitral or aortic apparatus or both resulting in insufficiency before adulthood. All the patients were homozygous for [D409H].
- Two patients (one from Jenin, one from Gaza) were affected with type II disease homozygous for the same mutation F331S (c.1109T>C)
- A severe neuronopathic form of Gaucher disease has been diagnosed in several patients from the **Territories** who are homozygous for [L444P]. The disease is very severe but the progression is less rapid than in the classical type II of the disorder.

References:

- Abramov A, Elstein D, Gross-Tsur V, Farber B, Glaser B, Hadas-Halpern I, Ronen S, Tafakjidi M, Horowitz M, Zimran A. Gaucher's disease variant characterized by progressive calcification of heart valves and unique genotype. *Lancet* 1995;346:1000-1002.
- Baris HN, Raas-Rothschild A, Garty BZ, Tor R, Klontz S, Tayebi N, Sidransky E, Cohen IJ. Gaucher disease type 2 - Homozygosity for the mutation F331S in two unrelated consanguineous Muslim Arab patients with Gaucher disease from the Gaza and Jenin regions. *Blood Cells Mol Dis*. 2011;47:262-263.
- Rockah R, Narinsky R, Hatskelzon L, Frisch A. type I Gaucher disease due to homozygosity for the 259T mutation in a Bedouin patient. *Am J Med Genet* 1997;72 77-78.

Generalized epilepsy with febrile seizures plus (GEFS+)

Autosomal dominant (MIM 604233)

Generalized epilepsy with febrile seizures plus (GEFS+) is a familial epilepsy syndrome characterized by the presence of febrile and afebrile seizures.

Molecular genetics:

GEFS2, sodium-channel $\alpha 1$ -subunit, *SCN1A* (chromosomal locus 2q)

A novel SCN1A mutation [4968C-G] was identified in a family of **Druze origin**.

References:

Wallace RH, Scheffer IE, Barnett S, Richards M, Dibbens L, Desai RR, Lerman-Sagie T, Lev D, Mazarib A, Brand N, Ben-Zeev B, Goikhman I, Singh R, Kremmidiotis G, Gardner A, Sutherland GR, George AL Jr, Mulley JC, Berkovic SF. Neuronal sodium-channel $\alpha 1$ -subunit mutations in generalized epilepsy with febrile seizures plus. *Am J Hum Genet* 2001;68:859-865.

Glaucoma congenital

Autosomal recessive (MIM 231300)

The ocular globe is usually large as a result of the increased intraocular pressure dating from intrauterine life (buphthalmos). In only about half of cases are both eyes involved, and males are affected somewhat more often than females. The canal of Schlemm is present and communicates normally with the veins. The defect is thought to involve the permeability of the trabeculum to aqueous humor

Epidemiology:

The disease has been diagnosed in several Muslim Arab families. Among the Bedouins in the Negev the incidence has been calculated to be 1:1200 live births.

Molecular genetics:

cytochrome P4501B1 gene (CYP1B1).

Several mutations have been characterized in the Bedouins from the Negev. The most frequent is [3987G>A] that account for 50% of the mutations (the same mutation is also found in 50% of the Bedouin patients from Saudia Arabia. A novel mutation was found in two unrelated Bedouin families [8405G>A]. In one of those families both mutations [3987G>A] and [8405G>A] were found in homozygosity.

The already known mutation [Arg469Trp] was found in a bedouin family from the Negev and in Muslim Arab Families as well as Druze families. Several other mutations were found among Muslims: [G61E] [p.Glu229Lys][p.Arg368His][907delG][1410-1422 del 13bp][p.R469W] and Druze[p.Met1Th][p.Pro289insC].

References:

Bar-Yosef U, Levy J, Elbedour K, Ofir R, Carmi R, Birk OS. Congenital Glaucoma: CYP1B1 Mutations in Israeli Bedouin Kindreds. J Glaucoma 2010;19:35-38.
Geyer O, Wolf A, Levinger E, Harari-Shacham A, Walton DS, Shochat C, Korem S, Bercovich D. Genotype/Phenotype Correlation in Primary Congenital Glaucoma Patients From Different Ethnic Groups of the Israeli Population. Am J Ophthalmol 2011;151:263-271.

Glucose-galactose malabsorption

Autosomal recessive (MIM 606824)

The intestinal monosaccharide transporter deficiency known as glucose/galactose malabsorption (GGM) produces a clinical picture indistinguishable from that of intestinal disaccharidase deficiency. The disorder manifests itself within the first weeks of life. The consequent severe diarrhea and dehydration are usually fatal unless glucose and galactose are eliminated from the diet. Almost all patients with glucose/galactose malabsorption show a slight, intermittent glucosuria. There seems to be a clinical remission with increased age in severe glucose/galactose malabsorption even though active jejunal glucose transport remained absent.

Epidemiology:

The disease has been diagnosed in three children from a Muslim Arab family in a town of **central Israel**.

Molecular genetics:

SGLT1, intestinal sodium/glucose co transporter gene (chromosomal locus 22q13.12).

The patients were homozygous for a missense mutation [C255W].

References:

Kesselman D, Reish O, Gal N, Gore H, Bujanover Y, Anikster Y. Molecular Basis for Glucose-Galactose Malabsorption In Large Kindred. ASHG meeting 2004

Glutaric acidemia type I

Autosomal recessive (MIM 231670)

Patients present during the first year of life with an acute encephalitis like disease associated with an intercurrent infection, On recovery of the acute disease, multiple neurologic abnormalities including quadriplegia, choreoathetosis and dystonic posturing persist in most patients. Clinical variability is common and some develop insidiously dystonia and choreoathetosis while other remain asymptomatic.

Glutaric aciduria type I is an inborn error of metabolism due to the deficiency of the mitochondrial enzyme glutaryl-CoA dehydrogenase (GCD). GCD is a mitochondrial homotetramer that dehydrogenates glutaryl CoA to crotonyl CoA in the oxydation pathway of lysine, hydroxylysine and tryptophan in the mitochondria. The result of the enzymatic reaction is the reduction of the enzyme bound flavin adenine diphosphate.

Epidemiology:

The disease has been diagnosed in several Arab families from the **Hebron area** and in the **North of Israel** and in **Jerusalem**.

Molecular genetics:

glutaryl-CoA dehydrogenase gene, GCD (chromosomal locus 19p13.2).

The mutations which were found in the Arab patients were [1173delG], a frame shift deletion [T416I], [L283P], [G101R], [A293T], [S305L] and [G390R].

The mutation [T416I] was diagnosed in several families from Jerusalem where other mutations were also found [N393S], [A293T] and [T193-R194 insH]

References:

Anikser Y, Shaag A, Joseph A, Mandel H, Ben-Zeev B, Christensen E, Elpeleg ON. glutaric aciduria type I in the Arab and Jewish communities in Israel. Am J Hum Genet 1996; 59:1012-1018.

Korman SH, Jakobs C, Darmin PS, Gutman A, van der Knaap MS, Ben-Neriah Z, Dweikat I, Wexler ID, Salomons GS. Glutaric aciduria type I: Clinical, biochemical and molecular findings in patients from Israel. Eur J Paediatr Neurol. 2007;11:81-89.

Glutaric acidemia type II

Multiple ACYL-CoA dehydrogenation deficiency MADD

Autosomal recessive (MIM 231680)

Glutaricaciduria II is an autosomal recessively inherited disorder of fatty acid, amino acid, and choline metabolism. It differs from GA I in that multiple acyl-CoA dehydrogenase deficiencies result in large excretion not only of glutaric acid, but also of lactic, ethylmalonic, butyric, isobutyric, 2-methyl-butyric, and isovaleric acids. GA II results from deficiency of any 1 of 3 molecules: the alpha (ETFA) and beta (ETFB) subunits of electron transfer flavoprotein, and electron transfer flavoprotein dehydrogenase (ETFDH). The clinical picture of GA II due to the different defects appears to be nondistinguishable.

Typical clinical features of the disorder are respiratory distress, muscular hypotonia, sweaty feet odor, hepatomegaly, and death often in the neonatal period.

Epidemiology:

The disease has been diagnosed in two families of Palestinian Arabs one living in the North of Israel.

Molecular genetics:

GA IIA, *ETFA* gene (chromosomal locus 19q13.3

GA IIB, *ETFB* gene (chromosomal locus 15q23-q25)

GA IIC, *ETFDH* gene (chromosomal locus 4q32-qter).

The mutations which were found in the Arab patients were in the *ETFDH* gene: one was homozygote for 1074G>C and the other was compound heterozygote 299T>A and 1425C>A

References:

Olsen RK, Andresen BS, Christensen E, Mandel H, Skovby F, Nielsen JP, Knudsen I, Vianey-Saban C, Simonsen H, Gregersen N. DNA-based prenatal diagnosis for severe and variant forms of multiple acyl-CoA dehydrogenation deficiency. *Prenat Diagn.* 2005; 25:60-64.

Glycogen storage disease type 1a

Autosomal recessive (MIM 232200)

The disease manifests itself usually in the first year of life by severe hypoglycemia, hepatomegaly, growth deficiency and bleeding diathesis. Long term complications include gout, hepatic adenomas, osteoporosis and renal disease. Type 1a represent 80-90% of the patients with glycogen disease type I and is secondary to the deficiency of the microsomal glucose 6 phosphatase (G6Pase) activity. The deficiency may be demonstrated in liver biopsy.

Epidemiology:

The disease has been reported in several families.

Molecular genetics:

Glucose 6 phosphatase gene (chromosomal locus 17q21)

One Muslim Arab patient from the Galilee was reported homozygous for a missense mutation [V66G].

References:

- Lei KJ, Shelly LL, Chen YT, Chen H, Wong LJC, Liu JL, Mcconkie-Rosell A, van Hove JLK, Ou HCY, Yeh NJ, Pan CJ, Chou J. Genetic basis of glycogen storage disease type 1a: prevalent mutations at the glucose-6-phosphatase locus. *Am J Hum Genet* 1995;57:34-41.
- Parvari R, Lei KJ, Bashan N, HersHKovitz E, Korman SH, Barash V, Lerman-Sagie T, Mandel H, Chou JY, Moses SW. Glycogen storage disease type 1a in Israel: biochemical, clinical and mutational studies. *Am J Med Genet* 1997; 72:286-290.

Glycogen storage disease type 1b

Autosomal recessive (MIM 232220)

The disease manifests itself usually in the first year of life by severe hypoglycemia, hepatomegaly, growth deficiency and bleeding diathesis as in type 1a. In addition, the patients suffer additional infectious complications that are due to the heritable neutropenia and the functional deficiency of neutrophils and monocytes.

Epidemiology:

Several **Arab and Bedouin** families have reported from Israel.

Molecular genetics:

G6PT gene (chromosomal locus 11p23).

Among the Bedouin families 2 different mutations in the G6PT gene were characterized [1211delCT] in one family and [R28H] in 2 families. Among Arab patients, 2 other mutations were characterized [W393X] and [G149E].

References:

Anabi B, Hiraiwa H, Mansfield BC, Lei KJ, Ubagai T et al. The gene for glycogen storage disease type 1b maps to chromosome 11p23. *Am J Hum Genet* 1998 62:400-405.
Hiraiwa H, Pan CJ, Lin B, Moses SW, Chou JY. Inactivation of the glucose 6-phosphate transporter causes glycogen storage disease type 1b. *J Biol Chem* 1999; 274:5532-5536.

Glycogen storage disease type II (Pompe disease)

Autosomal recessive (MIM 232300)

The classical phenotype is characterized by early infantile onset with hepatic, skeletal and cardiac muscular onset with rapid progression to death before the age of 2. The presentation is usually severe hypotonia and cardiomyopathy. The biochemical basis of the disease is the deficiency of the lysosomal enzyme alpha glucosidase (acid maltase) which leads to the accumulation of glycogen.

Epidemiology:

The disease is relatively frequent among non-Jews in Israel and in a survey of all the patients diagnosed in a 15 years period most were Arabs, affected with the infantile form of the disease. The juvenile form of Pompe disease has been diagnosed in Druze patients from one village.

In a large Druze Kindred from Northern Israel infantile and Juvenile-onset Glycogen Storage Disease type II

Molecular genetics:

Acid alpha glucosidase gene GAA (chromosomal locus 17q252-q253)

In the large Druze Kindred Two missense mutations were identified: [D404N] and [L355P] without a clear genotype phenotype correlation.

In a Muslim Arab family from central Israel Lys114fsTer31.

References:

- Bashan N, Potashnik R, Barash V, Gutman A, Moses SW. Glycogen storage disease type II in Israel. *Isr J Med Sci* 1988;24:224-227.
- Mandel H, Shochat C, Korem S, Sanas L, Mesika O, Gershoni-Baruch R, Bercovich D. Infantile and Juvenile-onset Glycogen Storage Disease type II in a Druze Kindred from Northern Israel: Genotype Phenotype Correlation. Meeting ASHG 2004.
- Hermans MM, van Leenen D, Kroos MA, Beesley CE, Van Der Ploeg AT, Sakuraba H, Wevers R, Kleijer W, Michelakakis H, Kirk EP, Fletcher J, Bosshard N, Basel-Vanagaite L, Beesley G, Reuser AJ. Twenty-two novel mutations in the lysosomal alpha-glucosidase gene (GAA) underscore the genotype-phenotype correlation in glycogen storage disease type II. *Hum Mutat* 2004; 23:47-56.

Glycogenosis V, myophosphorylase deficiency, McArdle disease

Autosomal recessive (MIM 232600)

McArdle disease is a disorder of muscular glycogen metabolism characterized by exercise intolerance, muscle pain and stiffness on exertion.

Epidemiology:

One **Druze family** was reported in which the disease occurred in three generations

Molecular genetics:

PYGM gene glycogen myophosphorylase is localized to 11q13.

A G to A transition [18844+1G→A] was found in all the patients in the Druze family, implying therefore a high carrier frequency in the kindred.

References:

Iyengar S, Kalinsky H, Weiss S, Korostishevsky M, Sadeh M, Zhao Y, Kidd KK, Bonne-Tamir B. Homozygosity by descent for a rare mutation in the myophosphorylase gene is associated with variable phenotypes in a Druze family with McArdle disease. *J Med Genet* 1997;34:391-394.

GM1 gangliosidosis

Autosomal recessive (MIM 230500)

The features are: (1) severe cerebral degeneration leading to death within the first 2 years of life; (2) accumulation of ganglioside in neurons, and in hepatic, splenic and other histiocytes, and in renal glomerular epithelium; and (3) the presence of skeletal deformities resembling Hurler disease. The ganglioside stored is different from that in Tay-Sachs disease and was identified as a GM1) ganglioside. Many patients have alteration in the lumbar vertebrae and cherry spots on the retina and angiokeratoma corporis diffusum may be present.

Epidemiology and Molecular genetics:

beta-galactosidase-1 gene GAA (chromosomal locus 3p21.33)

The disease has been diagnosed in several Muslim patients with the mutationa: p.H276P; p.K346N ; p.R201H

Griscelli syndrome

Autosomal recessive (MIM 214450)

In 4 patients exhibited a range of neurologic involvement from mild cognitive delay with a convulsive disorder in one patient to a fatal degenerative course in 3 others. They had highly variable neurologic involvement, along with the hemophagocytic syndrome and immunologic abnormalities. This family included 4 affected children: a brother (the proband) and sister in one family, and their 2 female first cousins. All 4 individuals died in childhood, at ages 11.5 years, 10 months, 6 years, and 2 years, respectively. All had silvery hair. Skin biopsies revealed normal numbers of melanocytes containing normally sized melanin granules. The 3 females presented with recurrent vomiting; the sister of the proband had an acute febrile illness, and 1 of her cousins presented with lethargy. All 3 deteriorated neurologically after their initial presentation, as indicated by regression of mental and physical function. The clinical course of the proband was characterized by periodic episodes of seizures, from the age of 1 year, and by mild cognitive delay. At the age of 2 years 10 months, he experienced an episode similar to the accelerated phase and recovered completely. He was well and had no recurrent infections and his neurologic status was stable until age 8 years. He was not monitored between the ages of 8 years and 10.5 years, after which he was repeatedly admitted to a local hospital because of prolonged fever, severe hepatosplenomegaly, and pancytopenia. His condition deteriorated, and he developed ascites, generalized edema, and jaundice and died at the age of 11.5 years.

Epidemiology

The disorder was described in one consanguineous Palestinian family

Molecular genetics

RAB27A gene (chromosomal locus 15q21)

The patients have normal MYO5A genes but exhibit a homozygous 67.5-kb deletion that eliminates RAB27A mRNA and immunocytofluorescence-detectable protein.

References

Anikster Y, Huizing M, Anderson PD, Fitzpatrick DL, Klar A, Gross-Kieselstein E, Berkun Y, Shazberg G, Gahl WA, Hurvitz H. Evidence that with neurological involvement is caused by mutations in RAB27A, not MYO5A. *Am J Hum Genet.* 2002; 71:407-4014.

Gray platelet syndrome

Autosomal dominant (MIM 139090)

Gray platelet syndrome is a usually mild to moderate bleeding disorder. The disease has been diagnosed in several members of a small Bedouin tribe in the North of Israel often with myelofibrosis. The disorder has been reported as autosomal dominant trait, but in several cases including the Bedouin pedigree a recessive inheritance was suggested since the parents of the affected individuals were normal.

Thrombocytopenia, abnormally large, agranular, gray platelets are found by routine staining and almost total absence of platelets alpha granules and their constituents.

Epidemiology:

The disease has been diagnosed in several members of a **small Bedouin tribe in the North** of Israel. It has been also reported in a Palestinian family from the Emirates.

Molecular genetics:

NBEAL2 (chromosomal location 3p21.1-p22.1)

All the patients from the Bedouin tribe are homozygous for c.2701C>T (p.Arg901X)

References:

Falick-Zaccai TC, Anisker Y, Rivera Y, McDonald K, Horne H, Schiamser L, Phornphutku C, Attias D, Hyman T, White JG, Gahl WA. A new genetic isolate of gray platelet syndrome (GPS). Clinical, cellular and hematologic characteristics. *Mol Genet Metabol* 2001;74:303-312.

Gunay-Aygun M, Falik-Zaccai TC, Vilboux T, Zivony-Elboum Y, Gumruk F, Cetin M, Khayat M, Boerkoel C F, Kfir N, Huang Y, Maynard D, Dorward H, Berger K, Kleta R, Anikster Y, Arat M, Freiberg AS, Kehrel BE, Jurk Kn, Cruz P, Mullikin JC, White JG, Huizing M, Gahl WA. NBEAL2 is mutated in gray platelet syndrome and is required for biogenesis of platelet α -granules. *Nature genetics* 2011;43:732-734.

Growth Hormone Deficiency Type Ib

Autosomal recessive (MIM 262400)

Isolated growth hormone deficiency (IGHD) Ib is characterized by a good response to exogenous growth hormone treatment without development of antibodies. This type of the disorder may be secondary rarely to mutations in GH1 gene and mainly in mutations in the growth hormone releasing receptor gene.

Epidemiology:

In an extended **Bedouin family from the Negev** an autosomal recessive form of IGHD due to a mutation in the GH-1 gene was diagnosed in several patients.

Several patients were diagnosed in two **Muslim Arab families** from the center of Israel without any known relation between the two.

Molecular genetics:

GH-1 gene (chromosomal locus 17q22-q24)

In the Bedouin kindred the patients are homozygous for a splicing mutation in the GH-1 gene (G→C transversion at the fifth base in the splice donor region of intron 4). In this family the carriers of the mutant allele were significantly shorter than the homozygous normal suggesting that some mutations in this gene may be implicated in reduced height in the population.

GHRH-R gene (chromosomal locus 7p15-p14)

In the two Muslim Arab families the patients are homozygous for R357C a mutation in the GHRH-R gene. In a sample of 50 unaffected Arabs, 2 were carriers.

References:

- Abdul-Latif H, Leiberman E, Brown MR, Carmi R, Parks JS. Growth hormone deficiency type Ib caused by cryptic splicing of the GH-1 gene. *J Pediatr Endocr Metabol* 2000;13:21-28.
- Haskin O, Lazar L, Jaber L, Salvatori R, Alba M, Kornreich L, Phillip M, Gat-Yablonski G. A new mutation in the growth hormone-releasing hormone receptor gene in two Israeli Arab families. *J Endocrinol Invest*. 2006; 29:122-130.
- Leiberman E, Pesler D, Parvari R, Elbedour K, Abdul-Latif H, Brown MR, Parks JS, Carmi R. Short stature in carriers of recessive mutation causing familial isolated growth hormone deficiency. *Am J Med Gen* 2000;90:188-192.

H syndrome

Autosomal recessive (MIM 612391)

The patients present with hyperpigmented, hypertrichotic, and indurated cutaneous patches involving the middle and lower parts of their bodies. Additional findings are short stature, sensorineural hearing loss, cardiac anomalies, hepatosplenomegaly, and scrotal masses. The cutaneous findings are progressive, beginning on the medial thighs and gradually spreading downward to involve the shins and feet and upward to involve the lower and middle aspects of abdomen. Gradual worsening of hearing loss is also seen. Laboratory evaluation suggested an inflammatory nature of the disease process, combined with endocrine dysfunction resulting in short stature, borderline hypergonadotropic hypogonadism, and azoospermia. Radiologic imaging shows massive infiltration of the subcutis that, by histopathologic evaluation, was found to be composed of histiocytic infiltrates in the dermis and subcutis, accompanied by plasma cells and mast cells.

Epidemiology:

The syndrome was reported in 10 Muslim Arab families from Jerusalem and the region in the West Bank. Two mutations in the SLC29A3 was found in 1% of individuals from the region.

Molecular genetics:

SLC29A3(hENT3) gene (chromosomal locus 10q21.3-q22.1)

In three families the patients were homozygous for c.1279G>A [G427S], in two families for c.1309G>A [G437R], in the last family the patient was compound heterozygous for the two mutations. Another mutation was found in a Muslim patient

References:

Molho-Pessach V, Agha Z, Aamar S, Glaser B, Doviner V, Hiller N, Zangen DH, Raas-Rothschild A, Ben-Neriah Z, Shweiki S, Elpeleg O, Zlotogorski A. The H syndrome: A genodermatosis characterized by indurated, hyperpigmented, and hypertrichotic skin with systemic manifestations. *J Am Acad Dermatol.* 2008;59:79-85. Epub 2008 Apr 14
Molho-Pessach V, Lerer I, Abeliovich D, S, Agha A, Abulibdeh A, Broshtilova V, Elpeleg O, Zlotogorski A. The H syndrome is caused by mutations in the nucleotide transported hENT3. *Am J Hum Genet* 2008;83:529-534.

Hemolytic uremic syndrome, Complement H factor 1 deficiency

Autosomal recessive (MIM 235400)

Ten children from a large inbred **Bedouin kindred from the Negev** were reported with an autosomal recessive form of the hemolytic uremic syndrome. The patients were diagnosed in rule in the first weeks of life (range 1-20 weeks), one of them died at home at the age of 3 weeks. On admission, all the patients presented with elevated serum creatinine and microangiopathic fragmentation of red blood cells. Usually the patients were very ill at the presentation, with oliguria, edema and severe hypertension. Four of the children had pulmonary edema necessitating assisted ventilation. Several patients had relapse and most died in the first months of life. The two surviving patients had several episodes and were dialysis dependent at the time of the report.

All patients had low complement component levels during and between the relapses and in some this was even evidence before the appearance of the symptoms. Serum factor H levels were decreased or absent in all the patients tested while the biosynthesis of C3 was normal in fibroblasts. It is speculated that the basic defect may be complement activation and consumption possibly at the endothelial cell level.

Epidemiology:

The syndrome has been reported in a single **Bedouin tribe from the Negev**.

Molecular genetics:

Complement factor H gene CFH (chromosomal locus 1q32)

A single mutation a T substitution and a 24 bp deletion was found in homozygosity in all the patients. The effect of the mutation is to replace at least 7AA of the protein with three different AA and most importantly it deletes the final cysteine residue.

References:

- Buddles MRH, Done RL, Richars A, Gooship J, Goodship THJ. Complement factor H gene mutation associated with autosomal recessive atypical hemolytic uremic syndrome. *Am J Hum Genet* 2000;66:1721-1722.
- Ohali M, Shalev H, Schlesinger M, Katz Y, Kachko L, Carmi R, Landau D. Hypocomplementemic autosomal recessive hemolytic uremic syndrome with decreased factor H. *Pediatr Nephrol* 1998;12:619-624.
- Ying L, Katz Y, Schlesinger M, Carmi R, Shalev H, Haider N, Beck G, Sheffield VC, Landau D. Complement factor H gene mutation associated with autosomal recessive atypical hemolytic uremic syndrome. *Am J Hum Genet.* 1999; 65:1538-1546.

Hereditary haemorrhagic telangiectasia

Autosomal dominant (MIM 187300)

Hereditary haemorrhagic telangiectasia (HHT or Rendu-Osler-Webersyndrome is characterised by vascular dysplasia and is inherited in an autosomal dominant manner. HHT occurs among many ethnic groups over a wide geographical area. In most cases, the manifestations of HHT are not present at birth, but develop with age; epistaxis is usually the earliest sign, often occurring in childhood, while mucocutaneous and gastrointestinal telangiectases develop progressively with age. Arteriovenous malformations in the pulmonary, cerebral, or hepatic circulations account for some of the most devastating clinical complications of HHT and are due to direct connections between arteries and veins. The shunting of blood through these lesions can lead to serious complications such as hypoxemia, stroke, brain abscess, heart failure, and fatal haemorrhage.

Epidemiology:

Epidemiological studies have revealed an incidence for this disease of 1 in 5000–8000. The disorder has been reported in a family from the North of Israel.

Molecular genetics:

Endoglin gene ENG (chromosomal locus)

A single mutation c932T→G in exon 7 was found in all the affected. Even though there were consanguineous marriages, no live individual homozygous for the mutation was found.

References:

Karabegovic A, Shinawi M, Cymerman U, Letarte M. No live individual homozygous for a novel *endoglin* mutation was found in a consanguineous Arab family with hereditary haemorrhagic telangiectasia. *J Med Genet* 2004;41: e119

Hereditary lymphedema type I

Autosomal dominant (MIM 153100)

Hereditary lymphedema type I (HL-I), also known as Milroy disease, is an autosomal dominant disorder characterized by typical phenotype of infantile onset lower-limb lymphedema accompanied by variable expression of recurrent episodes of cellulites, toe nail changes, and papillomatosis. In the family most affected individuals presented with bilateral congenital lower-limb lymphedema. Wide intrafamilial phenotypic variability included two asymptomatic individuals, a case of prenatal hydrothorax evolving to hydrops fetalis.

Epidemiology:

The disease has been reported in **a Muslim Arab family from the Galilee**

Molecular genetics:

Vascular endothelial growth factor receptor 3 (VEGFR3) gene (chromosomal locus 5q35.3)

Genetic analysis revealed novel missense mutation [E1106K] in the tyrosine kinase domain II of VEGFR3 that cosegregates with the disorder in the family.

References:

Spiegel R, Ghalamkarpour A, Daniel-Spiegel E, Vikkula M, A Shalev S. Wide clinical spectrum in a family with hereditary lymphedema type I due to a novel missense mutation in VEGFR3. *J Hum Genet.* 2006;51:846-850.

Hereditary non-polyposis colon cancer

Autosomal dominant (MIM 120435)

Hereditary Non-Polyposis Colorectal Cancer (HNPCC, Lynch syndrome) is an autosomal dominant cancer predisposition syndrome associated with a high life-time risk for colorectal cancer (up to 80%), endometrial cancer (up to 60%), and increased risk for other malignancies, mostly ovarian and urinary system tumors.

Molecular genetics:

HNPCC is caused by a germline mutation in one of the mismatch repair (MMR) genes (hMLH1, hMSH2, hMSH3, hMSH6, hPMS1, hPMS2). Loss of function in one of these key genes leads to 100-fold increased mutability.

A founder mutation in MSH2 was found among the Druze c.702delA (p.Thr234fsX245).

References:

Zidan J, Niessen RC, Laitman Y, Rozeveld D, Hofstra RM, Friedman E. A novel MSH2 germline mutation in a Druze HNPCC family. *Fam Cancer*. 2008;7:135-139.

Hermansky-Pudlak syndrome

Autosomal recessive (MIM 203300)

Hermansky-Pudlak syndrome is a disorder of the formation of intracellular vesicles. Patients exhibit various degrees of oculocutaneous albinism with congenital nystagmus, hypopigmentation of the skin, hair and irides. The platelets lack the dense bodies, accounting for the loss of secondary aggregation and for subsequent bleeding of mucous membranes and soft tissues. The diagnosis is based on the absence of dense granules in platelets in EM.

In the Bedouin family the phenotype resembles to Oculocutaneous albinism.

Epidemiology:

The disease has been reported in a **Bedouin tribe from the Negev**

Molecular genetics:

HPS6 gene (chromosomal locus 3q24)

A unique HPS6 mutation has been found among the Bedouin patients [c.1066_1067insG].

References:

Schreyer-Shafir N, Huizing M, Anikster Y, Nusinker Z, Bejarano-Achache I, Maftzir G, Resnik L, Helip-Wooley A, Westbroek W, Gradstein L, Rosenmann A, Blumenfeld A. A new genetic isolate with a unique phenotype of syndromic oculocutaneous albinism: clinical, molecular, and cellular characteristics. *Human Mutation* 2006. Mutations in brief # 934

Hereditary spastic paraplegia

Autosomal recessive (MIM 604360)

The disease was reported in 3 brothers from a Muslim family from Jerusalem. In all patients gait disturbance was first noted at 10-13 years of age which progressed slowly.

Epidemiology and Molecular genetics:

KIF1A (chromosomal locus 2q37.3)

The mutation Ala255Val was characterized in one Muslim family from Jerusalem

References:

Erlich Y, Edvardson S, Hodges E, Zenvirt S, Thekkat P, Shaag A, Dor T, Hannon GJ, Elpeleg O. Exome sequencing and disease-network analysis of a single family implicate a mutation in KIF1A in hereditary spastic paraparesis. *Genome Res.* 2011;21:658-664.

Hereditary spastic paraplegia, type 11

Autosomal recessive (MIM 604360)

The disease was reported in 3 consanguineous Arab-Israeli families. All patients had onset of clinical symptoms during the second decade of life, with cognitive decline preceding gait disturbance by 2 to 5 years. Cardinal signs included pseudobulbar dysarthria, spastic paraparesis with lower limb hyperreflexia, upper limb hyperreflexia, extensor plantar responses, and distal amyotrophy

Epidemiology:

The syndrome has been reported in three Arab families.

Molecular genetics:

SPG11 gene (chromosomal locus 15q13-q15)

The mutation Q40X was characterized in one Bedouin family from the Galilee.

References:

Lossos A, Stevanin G, Meiner V, Argov Z, Bouslam N, Newman JP, Gomori JM, Klebe S, Lerer I, Elleuch N, Silverstein S, Durr A, Abramsky O, Ben-Nariah Z, Brice A. Hereditary spastic paraplegia with thin corpus callosum: reduction of the SPG11 interval and evidence for further genetic heterogeneity. *Arch Neurol.* 2006;63:756-760.

Stevanin G, Santorelli FM, Azzedine H, Coutinho P, Chomilier J, Denora PS, Martin E, Ouvrard-Hernandez AM, Tessa A, Bouslam N, Lossos A, Charles P, Loureiro JL, Elleuch N, Confavreux C, Cruz VT, Ruberg M, Leguern E, Grid D, Tazir M, Fontaine B, Filla A, Bertini E, Durr A, Brice A. Mutations in SPG11, encoding spatacsin, are a major cause of spastic paraplegia with thin corpus callosum. *Nat Genet.* 2007;39 :366-372.

Hereditary spastic paraplegia SPG15

Autosomal recessive (MIM 270700)

The hereditary spastic paraplegias (HSPs) are inherited neurological disorders characterized by progressive lower-limb spasticity, with an estimated prevalence of 1.27–9.6/100,000. The disease is characterized pathologically by axonal degeneration in the long ascending and descending tracts of the spinal cord, especially in their terminal portions, associated with syndrome-specific degeneration of other structures. Although the corticospinal tracts are predominantly affected, the columns of Goll and the spinocerebellar tracts are also involved.

SPG15, is a “complicated” AR-HSP, that was initially identified in association with pigmentary maculopathy (Kjellin syndrome; MIM 270700). Later it was demonstrated that the clinical features varied among patients and families and cognitive impairment and distal amyotrophy were frequent. Peripheral neuropathy, maculopathy, cerebellar ataxia, thin corpus callosum, and white matter abnormalities on MRI were also observed but are not constant clinical features of the disease.

Epidemiology and Molecular genetics:

SPG15 gene (chromosomal locus 14q23.3-q24.2)

The mutation c.6702_6771 del was identified in homozygosity in patients from a large Muslim Arab family.

References:

Hanein S, Martin E, Boukhris A, Byrne P, Goizet P, Hamri A, Benomar A, Lossos A, Denora P, Fernandez, Elleuch JN, Forlani S, Durr A, Feki I, Hutchinson M, Santorelli FM, Mhiri C, Brice A, Stevanin G. Identification of the SPG15 Gene, Encoding Spastizin, as a Frequent Cause of Complicated Autosomal-Recessive Spastic Paraplegia, Including Kjellin Syndrome. *Am J Hum Genet* 2008; 82:992-1002

Hirschsprung's disease

Hirschsprung disease or aganglionic megacolon is a congenital disorder characterized by absence of enteric ganglia along a variable length of the intestine. Most affected children fail to pass meconium in first 48 hours of life and abdominal distention is an early symptom. Barium enema shows transition zone between aganglionic contracted segment and dilated proximal bowel.

Epidemiology:

The disease has been reported in a group of patients originating from **Bedouin families from the Negev** and in a **large Muslim Arab kindred** from the center of Israel.

Molecular genetics:

RET gene (chromosomal locus 10q11.2)

A unique mutation has been found in the family from central Israel [p.IVS6+5G>A].

References:

Halevy H, Mares A, Cohen Z, Finaly R, Freud E, Pilpel D. Hirschsprung's disease in the Negev. Harefuah 1994;127:148-154.

Basel-Vanagaite L, Pelet A, Steiner Z, Munnich A, Rozenbach Y, Shohat M, Lyonnet S. Allele dosage-dependent penetrance of RET proto-oncogene in an Israeli-Arab inbred family segregating Hirschsprung disease. Eur J Hum Genet. 2007; 15:242-245.

Homocystinuria

Autosomal recessive (MIM 236200)

The major clinical features are mental retardation, ectopia lentis, skeletal abnormalities and life threatening thrombotic events.

Homocystinuria is caused by deficient activity of one of several enzymes in methionine metabolism, either as a primary defect or as a result of defects in the cystolic metabolism of cobalamine.

Epidemiology:

The disease has been diagnosed in several Arab families in Israel either because of methylenetetrahydrofolate reductase deficiency, cystathionine β -synthetase deficiency or Cobalamin defect.

Molecular genetics:

CBS gene (chromosomal locus 21q223)

In one kindred all the patients were homozygous for two mutations on the same allele K102Q and a 29bp deletion in IVS4 leading to exon 5 skipping. In another village the patients were also homozygous for a double mutation a 19bp deletion in exon 16 and a deletion of the 5' of IVS17. In addition, in two other patients were homozygous for other mutations [I278T] and [T262R].

References:

Mandel H, Brenner B, Berant M, Rosenberg N, Lanir N et al. Coexistence of hereditary homocystinuria and factor V Leiden- effect on thrombosis. New Engl J Med 1996;334:763-768.

Gat-Yablonski, Mandel H, Fowler B, Taleb O, Sela BA. Homocystinuria in the Arab population in Israel: identification of two novel mutations using DGCE analysis. Human Mutation, Mutation in brief 2000 online #368.

Hurler syndrome

Autosomal recessive (MIM 607014)

Hurler syndrome, (mucopolysaccharidosis type I) is usually diagnosed in the first year of life because of progressive hepatosplenomegaly, coarse facial features and skeletal changes. Corneal opacities are most often present early in the course of the disease while retinal degeneration develops with time. The disease is progressive leading to severe disability and mental retardation.

Epidemiology:

Hurler syndrome is frequent among non-Jews in the **Galilee**. The highest incidence of the disease is found among **Druze** but the disease is also present among **Muslim** Arabs

Molecular genetics:

IDU gene (chromosomal locus 4p16.3)

Three different mutations were characterized: [THR366PRO], [TYR64TER] and [GLN310TER].

References:

Bach G., Moskowitz SM, Tieu PT, Matynia A, Neufeld EF. Molecular analysis of Hurler syndrome in Druze and Muslim Arab patients in Israel: multiple allelic mutations of the IDUA gene in a small geographic area. Am J Hum Genet 1993;53:330-338.

HUPRA syndrome (Hyperuricemia, Pulmonary Hypertension, Renal Failure in Infancy and Alkalosis)

Autosomal recessive (MIM)

The most striking features of the phenotype were prematurity, progressive renal disease, and primary pulmonary hypertension. Feeding problems, resulting in failure to thrive and developmental delay, were also noted without obvious morphological alterations in the brain after brain ultrasound.

Epidemiology:

The disease was reported in Muslim Arabs from a village within the Jerusalem municipality.

Molecular genetics:

SARS2 gene (chromosomal locus 19p)

All the patients were homozygous for the c.1169A>G mutation. The mutation was absent in 111 healthy unrelated individuals of Palestinian descent. Targeted screening of this mutation was found in 7 out of 103 individuals from the same village (1:15).

References:

Belostotsky R, Ben-Shalom E, Rinat C, Becker-Cohen R, Feinstein S, Zeligson S, Segel R, Elpeleg O, Nassar S, Frishberg Y. Mutations in the Mitochondrial Seryl-tRNA Synthetase Cause Hyperuricemia, Pulmonary Hypertension, Renal Failure in Infancy and Alkalosis, HUPRA Syndrome. *Am J Hum Genet* 2011; 88:193-200

Hydrocephalus,congenital

Autosomal recessive (MIM 236600)

Hydrocephalus is diagnosed either during the pregnancy or at birth. In most cases the pregnancy was interrupted or the affected children were stillborn. However, in some cases the children survived with severe mental retardation.

Epidemiology:

Isolated autosomal recessive congenital hydrocephalus has been reported in several families from the region of **Jerusalem/Hebron**. It seems that the prevalence of the disorder is relatively elevated in this population, as well as in other regions of Israel.

References:

Zlotogora J. Genetic disorders among the Palestinian Arabs. 2: neural tube defects and hydrocephalus. *Am J Med Genet* 1997;71:33-35.

Zlotogora J., Sagi M, Cohen T. Familial hydrocephalus of prenatal onset. *Am J Med Genet* 1994; 49:202-204.

Hypercholesterolemia, familial

Autosomal dominant (MIM 143890)

Familial hypercholesterolemia is an autosomal dominant disorder characterized by raised plasma LDL-C levels and is caused by mutations in the LDL receptor gene. The disease is prevalent in Lebanon and in Israel several families of **Christian Arabs** have been reported in which familial hypercholesterolemia was found because of the Lebanese allele: stop₆₆₀. Approximately 8% of the Christian Arab population in Israel is expected to be carrier of the Lebanese allele. Among Druze from the **Golan Heights** a same mutation [stop 167] was found in two unrelated families. In addition, 2 other alleles have been characterized among Muslim Arabs in Israel (FH Jerusalem [E187K], and [del 1165])

References:

- Landsberger D, Meiner V, Reshef A, Levy Y, van der Westhuyzen DR, Coetzee GA, Leitersdorf E. A nonsense mutation in the LDL receptor gene leads to familial hypercholesterolemia in the Druze sect. *Am J Hum Genet* 1992;50:427-433.
- Oppenheim A, Friedlander Y, Dann EJ, Beckman N, Pressman Schwartz S, Leitersdorf E. Hypercholesterolemia in five Christian Arab kindreds is caused by the "Lebanese" allele at the low density lipoprotein receptor gene locus and by an independent major factor. *Hum Genet* 1991;88:75-84.
- Reshef A, Nissen H, Triger L, Hensen TS, Eliav O, Schurr D, Safadi R, Gare M, Leitersdorf E. Molecular genetics of familial hypercholesterolemia in Israel. *Hum Genet* 1996;98:581-586.

Hyperchloridosis, autosomal recessive

Autosomal recessive (MIM 143860)

Cystic fibrosis (CF) is caused by mutations within the cystic fibrosis transmembrane conductance regulator (CFTR). Elevated levels of sweat electrolytes as measured in the "sweat test" are the classical routine diagnostic criterion for this disease. A Bedouin kindred in southern Israel presented with an autosomal recessive phenotype of elevated sweat electrolytes with no clinical evidence of CF .

Molecular genetics and epidemiology

CA12 (chromosome locus 15q22)

The syndrome was diagnosed in several patients from two Israeli-Bedouin kindreds from the Negev. In all the patients a homozygous missense mutation p.Glu433Lys was characterized. Of 300 Bedouin controls, the mutation was found in only one individual in a heterozygous state

References

- Feldshtein M, El-Krinawi S, Yerushalmi B, Landau D, Romi H, Marcus B, Vullo, Ofir R, Sivan S, Supuran CT., Birk OS. Hyperchlorhidrosis Caused by Homozygous Mutation in CA12, Encoding Carbonic Anhydrase XII. *Am J Hum Genet* 2010;87:713-720.
- Muhammad E, Leventhal N, Parvari G, Hanukoglu A, Hanukoglu I, Chalifa-Caspi V, Feinstein Y, Weinbrand J, Jacoby H, Manor E, Nagar T, Beck JC, Sheffield VC, HersHKovitz E, Parvari R. Autosomal recessive hyponatremia due to isolated salt wasting in sweat associated with a mutation in the active site of Carbonic Anhydrase 12. *Hum Genet.* 2011;129:397-405.

Hypertiglyceridemia, infantile transient

Autosomal recessive (MIM)

Molecular genetics and epidemiology

In a kindred of Muslim Arabs several individuals were affected with moderate to severe transient childhood hypertriglyceridemia with fatty liver and hepatic fibrosis. The oldest affected individual was 23 years of age at examination was asymptomatic with short stature, elevated transaminases and hyperechoic liver compatible with fatty changes.

GPD1 (chromosome locus 12q13/12)

All the affected were homozygous for c.361G>C p.Ile119fsX94 and the mutation was not found in a group of 404 random Arabs.

References

Basel-Vanagaite L, Zevit N, Zahav AH, Guo L, Parathath S, Pasmanik-Chor M, McIntyre AD, Wang J, Albin-Kaplanski A, Hartman C, Marom D, Zeharia A, Badir A, Shoerman O, Simon AJ, Rechavi G, Shohat M, Hegele RA, Fisher EA, Shamir R. Transient Infantile Hypertriglyceridemia, Fatty Liver, and Hepatic Fibrosis Caused by Mutated GPD1, Encoding Glycerol-3-Phosphate Dehydrogenase 1. *Am J Hum Genet.* 2012;90:49-60.

Hypocalciuric hypercalcemia

Autosomal recessive (MIM 145980)

This represents a relative benign condition in which the affected individual has hypocalciuric hypercalcemia.

Epidemiology:

The disease was reported in two related Bedouin Arab families from the Galilee.

Molecular genetics:

CASR gene (chromosomal locus 3q13.3-q21)

The patients were homozygous for [Q459R]

References

Lietman SA, Tenenbaum-Rakover Y, Jap TS, Yi-Chi W, De-Ming Y, Ding C, Kussiny N, Levine MA. 1. A Novel Loss-of-Function Mutation, Gln459Arg, of the Calcium-Sensing Receptor Gene Associated with Apparent Autosomal Recessive Inheritance of Familial Hypocalciuric Hypercalcemia. *J Clin Endocrinol Metab.* 2009;94:4372-4379.

Hypogonadotrophic hypogonadism

Autosomal recessive (MIM 146110)

GPR54 inactivation does not impede neuroendocrine onset of puberty; rather, it delays and slows down pubertal maturation of the gonadotropic axis

Epidemiology:

The disease was reported in a Muslim Arab family from the Galilee and a kindred in a village near the mediteranean coast.

Molecular genetics:

KISS1R/GPR54 gene (chromosomal locus 19p13.3)

in the village from the Galilee the patients were homozygous for [T305C] leading to a leucine substitution with proline [L102P]. The same mutation was found in an Arab family from Syria. In the kindred from the other village the patients were homozygous for c.T815C (p.F272S)

References

- Nimri R, Lebenthal Y, Lazar L, Chevrier L, Phillip M, Bar M, Hernandez-Mora E, de Roux N, Gat-Yablonski G. A Novel Loss-of-Function Mutation in GPR54/KISS1R Leads to Hypogonadotropic Hypogonadism in a Highly Consanguineous Family. *J Clin Endocrinol Metab* 2011; 96:E536-545. .
- Tenenbaum-Rakover Y, Commenges-Ducos M, Iovane A, Aumas C, Admoni O, de Roux N. Neuroendocrine phenotype analysis in five patients with isolated hypogonadotropic hypogonadism due to a L102P inactivating mutation of GPR54. *J Clin Endocrinol Metab*. 2007; 92:1137-1144. .

Hypophosphatasia, infantile

Autosomal recessive (MIM 241500)

Hypophosphatasia is a rare metabolic disorder characterized by low serum and tissue alkaline phosphatase activity, increased urinary excretion of phosphoethanolamine and ricketslike changes in the bone. Three more or less distinct types can be identified: (1) type 1 with onset in utero or in early postnatal life, craniostenosis, severe skeletal abnormalities, hypercalcemia, and death in the first year or so of life; (2) type 2 with later, more gradual development of symptoms, moderately severe 'rachitic' skeletal changes and premature loss of teeth; (3) type 3 with no symptoms, the condition being determined on routine studies. The clinical signs in the perinatal type of hypophosphatasia show considerable overlap with osteogenesis imperfecta congenita with achondrogenesis type IA. If present, spurs of the limbs are diagnostic for hypophosphatasia.

Epidemiology

The syndrome was reported in **three Muslim Arab families in the Galilee** and a **bedouin family of the Negev**.

Molecular genetics

ALPL gene (chromosomal locus 1p36.1-p34)

In two Muslim Arab families the same mutation was found R433C (Mandel, Shalev) . In another muslim family the mutation c.26C>A was characterized

References

Gortzak-Uzan L, Sheiner E, Gohar J. Prenatal diagnosis of congenital hypophosphatasia in a consanguineous Bedouin couple. A case report. J Reprod Med 2000;45:588-590

Hypomagnesemia, primary congenital

Autosomal recessive (MIM 602014)

The most common presenting events are generalized hypocalcemic-hypomagnesemic seizures in the first weeks of life (mean 5 weeks). The tetanic convulsions respond to parenteral magnesium and subsequently a good outcome is achieved with long term enteral magnesium. Failure of early diagnosis or non compliance to treatment may be detrimental causing permanent neurological damage.

Epidemiology:

The disease has been reported in a group of 15 patients originating from two large **Bedouin families from the Negev**. Two additional Arab families were reported from the Galilee.

Molecular genetics:

TRPM6 gene (chromosomal locus 9q22)

In the Bedouin families the mutation is 2009+1G-A. in one of the other Arab families from the North 1010+5G-C and the other family 3209-68A-G

References:

Shalev H, Phillip M, Galil A, Carmi R, Landau D. Clinical presentation and outcome in primary familial hypomagnesemia. Arch Dis Child 1998;78:127-130.
Walder RY, Landau D, Myer P, Shalev H, Tsolia M, Borochowitz Z, Boettger B, Beck GE, Engelhardt RK, Carmi R, Sheffield VC. Mutation of TRPM6 cause familial hypomagnesemia with secondary hypocalcemia. Nature Genet 2002;31:171-174.

Hypomyelination and Congenital Cataract

Autosomal recessive (MIM 610532)

In the original description bilateral congenital cataract was considered to be a major finding, and the neurologic picture was stereotyped: developmental delay was noticed at the end of the first year of life, the ability to walk was achieved during the second year with support only, and patients became wheelchair bound at the end of the first decade. However, it seems that cataract is not invariably congenital, and the age at neurologic presentation and the severity of the neurologic impairment varies. The MRI features of hypomyelination combined with increased periventricular white matter water content are consistently observed, distinguishing HCC from other forms of hypomyelinating leukoencephalopathies.

The most common presenting events are generalized hypocalcemic-hypomagnesemic seizures in the first weeks of life. The tetanic convulsions respond to parenteral magnesium and subsequently a good outcome is achieved with long term enteral magnesium. Failure of early diagnosis or non compliance to treatment may be detrimental causing permanent neurological damage.

Epidemiology and molecular genetics:

FAM126A gene (chromosomal locus 7p15)

The disease has been reported in one Arab family the patient was homozygous for c.649C>T (p.Arg217X)

References:

Traverso M, Yuregir OO, Mimouni-Bloch A, Rossi A, Aslan H, Gazzerro E, Baldassari S, Fruscione F, Minetti C, Zara F, Biancheri R. Hypomyelination and congenital cataract: Identification of novel mutations in two unrelated families. *Eur J Paediatr Neurol.* 2013;17:108-111.

Hypoparathyroidism, congenital, growth and mental retardation and dysmorphism

Autosomal recessive (MIM 241410)

The affected children present with either seizures or persistent hypocalcemia in the neonatal period or failure to thrive in the first months of life. Many dysmorphic features were noted in particular microcephaly, deep set eyes, depressed nasal bridge, retromicrognathia, abnormal dentition and delayed eruption of the teeth. The psychomotor development was severely impaired in all patients and axial hypotonia was a common finding. In all the children the presence of abnormal PTH plasma concentration with hypocalcemia and hyperphosphatemia beyond 8 weeks of age established the diagnosis of permanent hypoparathyroidism

Molecular genetics and Epidemiology:

TBCE gene (chromosomal locus 1q42.43)

The syndrome was first reported among Arab children from the Gulf countries and then in Arab families from Israel (most were Bedouin from the **Negev**). All the patients of middle eastern origin and from Saudi were homozygous for the same 155-156 del mutation including patients with the Kenny-Caffey syndrome. In another tribe the mutation c.207-208delTA was characterized.

References:

- Hershkovitz E, Shalitin S, Levy J, Leiberman E, Weinshtock A, Varsano I, Gorodisher R. The new syndrome of congenital hypoparathyroidism, associated with dysmorphism, growth retardation and developmental delay- a report of 6 cases. *Isr J Med Sci* 1995; 31:293-297.
- Parvari R, Hershkovitz E, Grossman N, Gorodischer R, Loeys B, Zecic A, Mortier G, Gregory S, Sharony R, Kambouris M, Sakati N, Meyer BF, Al Aqeel AI, Al Humaidan AK, Al Zahrani F, Al Swaid A, Al Othman J, Diaz GA, Weiner R, Khan KTS, Gordon R, Gelb BD. Mutation of *TBCE* causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. *Nature Genet* 2002;32:448-452.

Hypothyroidism, congenital

Autosomal recessive (OMIM 274500)

The newborn screening for hypothyroidism in Israel allows for the estimation of the frequency congenital hypothyroidism in Israel. Hypothyroidism is more frequent among Arabs (1/2100 live births) than among Jews (1/3,000 live births). The high incidence among non-Jews is not at random since a very high incidence of congenital hypothyroidism (1/600 or higher) is found in several Arab villages in the **Galilee**, while in the other Arab localities the incidence is similar to the one of the Jewish population.

Molecular genetics

Thyroid peroxidase gene TPO (chromosomal locus 2p25)

Several mutations have been found [G493S], [R540X] representing 90% of the alleles and [S292F].

THS receptor (chromosomal locus 15q25.3-26.1)

Several mutations have been found on the same allele [c.267G>L (L89L)], [c.269/270AG>CT (Q90P)], [c.790C>T (P264S)] in a family from one village in the Galilee .

References

Kaiserman I, Siebner R, Sack J. Regional and temporal fluctuations in the incidence of congenital hypothyroidism in Israel. *J Endocrinol Invest* 199;18:595-601.

Sriphrapadang C, Tenenbaum-Rakover Y, Weiss M, Barkoff MS, Admoni O, Kawthar D, Caltabiano G, Pardo L, Dumitrescu AM, Refetoff S. The Coexistence of a Novel Inactivating Mutant Thyrotropin Receptor Allele with Two Thyroid Peroxidase Mutations: A Genotype-Phenotype Correlation. *J Clin Endocrinol Metab.* 2011; 96:E1001-1006. .

Tenenbaum-Rakover Y, Mamasani S, Ris-Stalpers C, German A, Sack J, Allon-Shalev S, Pohlenz J, Refetoff S. Clinical and genetic characteristics of congenital hypothyroidism due to mutations in the thyroid peroxidase (TPO) gene in Israelis. *Clin Endocrinol (Oxf).* 2007; 66:695-702. .

Hypotrichosis simplex

Autosomal recessive (MIM 605389)

Autosomal recessive hypotrichosis simplex (ARHS) manifests with paucity of hair appearing during early childhood and progressing to adulthood. The extent of scalp and body hair is variable however hair is never totally absent.

Epidemiology:

Three Muslim Arab families from the lower Galilee.

Molecular genetics:

LIPH gene (chromosomal locus 3q27)

A homozygous duplication mutation in exon 2 (c.280_369dup; p.Gly94_Lys123dup) was found to segregate with the disease in all the families.

References

Nahum S, Pasternack SM, Pforr J, Indelman M, Wollnik B, Bergman R, Nöthen MM, König A, Khamaysi Z, Betz RC, Sprecher E. A large duplication in LIPH underlies autosomal recessive hypotrichosis simplex in four Middle Eastern families. *Arch Dermatol Res* 2009;301:391-393.

Hypotrichosis with juvenile macular dystrophy

Autosomal recessive (MIM 601553)

The affected are born with seemingly normal hair but develop alopecia at around 3 months. During puberty partial regrowth and sparse hair occur. In childhood adolescence the patients develop progressive macular degeneration with slight peripheral retinal dystrophy.

Epidemiology:

The syndrome was found in 4 Druze families from the Galilee. Among Muslim Arabs the disease has been reported in several villages

Molecular genetics:

CDH3 gene encoding P cadherin (chromosomal locus 16q22.1)

All the Druze patients were homozygous for 981delG mutation. The Muslim Arab patients were homozygous R503H or Y615X. In a Bedouin family the mutation c.747c>A was characterized.

References

- Indelman M, Bergman R, Lurie R, Richard G, Miller B, Petronius D, Ciubutaro D, Leibur R, Sprecher E. A Missense Mutation in CDH3, Encoding P-Cadherin, Causes Hypotrichosis with Juvenile Macular Dystrophy. *J Invest Dermatol* 2002;119:1210-1213.
- Indelman M, Leibur R, Jammal A, Bergman R, Sprecher E. Molecular basis of hypotrichosis with juvenile macular dystrophy in two siblings. *Br J Dermatol*. 2005;153:635-638.
- Sprecher E, Bergman R, Richard G, Lurie R, Shalev S, Petronius D, Shalata A, Anbinder Y, Leibur R, Perlman I, Cohen N, Szargel R. Hypotrichosis with juvenile macular dystrophy is caused by a mutation in CDH3 encoding P-cadherin. *Nature genetics* 2001;29:134-136.

Hypospadias

Autosomal recessive (MIM 271750)

Uncomplicated hypospadias was reported in several male members of a large Bedouin family. Virilization and fertility were normal in the only postpubertal male. Another Muslim Arab family was reported from Israel.

References

- Frydman M, Greiber C, Cohen HA. Uncomplicated familial hypospadias evidence for an autosomal recessive inheritance. *Am J Med Genet* 1985 21 51-60.
- Tsur M, Linder N, Cappis S. Hypospadias in a consanguineous family. *Am J Med Genet* 1987; 27:487-489.

Ichthyosis congenita, harlequin fetus type

Autosomal recessive (MIM 242500)

Harlequin ichthyosis (HI) is the most severe form of autosomal-recessive, congenital ichthyosis. Affected infants have markedly impaired barrier function and are more susceptible to infection. The baby is usually of low birth weight for dates and, as a rule, dies under 1 week of age. Plaques, measuring up to 4 or 5 cm on a side, have a diamond-like configuration resembling the suit of a harlequin clown. Tonofibrils are fibrillar structural proteins in keratinocytes which, although already present in dividing basal cells, are formed in increasing amounts by the differentiating cells. They are the morphologic equivalent of the biochemically well-characterized prekeratin and precursors of the alpha-keratin of horn cells. Four genetic disorders of keratinization are known to have a structural defect of tonofibrils.

Epidemiology:

The disease has been diagnosed in a Muslim Arab family.

Molecular genetics:

ABCA12 gene (chromosomal locus 2q34)

One patient was homozygous [Ex6_del]

References:

Thomas AC, Cullup T, Norgett EE, Hill T, Barton S, Dale BA, Sprecher E, Sheridan E, Taylor AE, Wilroy RS, Delozier C, Burrows N, Goodyear H, Fleckman P, Stephens KG, Mehta L, Watson RM, Graham R, Wolf R, Slavotinek A, Martin M, Bourn D, Mein CA, O'toole EA, Kelsell DP. ABCA12 Is the Major Harlequin Ichthyosis Gene. *Journal of Investigative Dermatology* 2006;126:2408-2413.

Ichthyosis autosomal recessive, late onset

Autosomal recessive

In the patients the skin looks normal at birth and the Ichthyosis develops later on the entire surface of the skin

Epidemiology:

The disease in a large kindred in a Muslim village from the Galilee.

Molecular genetics:

LIPN (chromosomal locus 10q23)

All the patients were homozygote for p.Glu133AspX3, c. 399-400delGA

References:

Israeli S, Khamaysi Z, Fuchs-Telem D, Nousbeck J, Bergman R, Sarig O, Sprecher E. A Mutation in LIPN, Encoding Epidermal Lipase N, Causes a Late-Onset Form of Autosomal-Recessive Congenital Ichthyosis. *Am J Hum Genet.* 2011;88:482-487.

Ichthyosis,exfoliative

Autosomal recessive (MIM 607936)

An unusual congenital ichthyosiform dermatosis was reported in 5 children from two related families of unaffected, consanguineous Bedouin parents. It appeared shortly after birth as a fine peeling of nonerythematous skin on palms and soles. Gradually it evolved into prominent, well-demarcated areas of peeling skin in moist and traumatized regions. The cutaneous manifestations share features of ichthyosis bullosa of Siemens (IBS) and peeling skin syndrome (PSS). Histologic examination revealed orthokeratosis, a thickened granular cell layer, and spongiosis without epidermolytic hyperkeratosis. On electron microscopy there was prominent intercellular edema and numerous aggregates of keratin filaments in basal keratinocytes. This combination of clinical, histologic, and ultrastructural features has not been previously reported in the heterogeneous group of congenital ichthyoses.

Epidemiology:

The disease in two related **Bedouins families from the Negev**.

Molecular genetics:

CSTA (*chromosomal locus 3q21*)

All the patients were homozygote for c.67-2A>T (p.Val23_Gln26del)

References:

Blaydon DC, Nitoiu D, Eckl KM, Cabral RM, Bland P, Hausser I, van Heel DA, Rajpopat S, Fischer J, Oji V, Zvulunov A, Traupe H, Hennies HC, Kelsell DP. Mutations in CSTA, encoding Cystatin A, underlie exfoliative ichthyosis and reveal a role for this protease inhibitor in cell-cell adhesion. *Am J Hum Genet.* 2011;89:564-471. Epub 2011 Sep 22.

Hatsell SJ, Stevens H, Jackson AP, Kelsell DP, Zvulunov A. An autosomal recessive exfoliative ichthyosis with linkage to chromosome 12q13. *Br J Dermatol.* 2003;149:174-180.

Ichthyosis with hypotrichosis syndrome

Autosomal recessive

A novel autosomal recessive ichthyosis syndrome featuring both ichthyosis and abnormal hair distribution and structure, have named "autosomal recessive ichthyosis with hypotrichosis syndrome." This disorder is clinically distinct from other genodermatoses involving skin and hair abnormalities. Compared with subjects affected with NTS, our patients have a milder disease, no erythrodermatous skin changes, no atopic manifestations, and no increased IgE

Epidemiology:

The disease in one **Muslim Arab family**.

Molecular genetics:

ST14, Encoding Type II Transmembrane Serine Protease Matriptase (chromosomal locus 11q24.3-q25)

All the patients were homozygous for G827R

References:

Basel-Vanagaite L, Attia R, Ishida-Yamamoto A, Rainshtein L, Ben Amitai D, Lurie R, Pasmanik-Chor M, Indelman M, Zvulunov A, Saban S, Magal N, Sprecher E, Shohat M. Autosomal Recessive Ichthyosis with Hypotrichosis Caused by a Mutation in ST14, Encoding Type II Transmembrane Serine Protease Matriptase. *Am J Hum Genet.* 2007; 80:467-477.

Inclusion Body Myopathy

Autosomal recessive (MIM 600737)

In most of the patients muscular weakness usually appears in the second half of the third decade as gait difficulties. The progression is gradual and most patients become severely incapacitated a decade after the onset. The most characteristic finding of the disease is preservation of the quadriceps. The quadriceps stay strong even in advanced stage of the disease and allow the patients to stand and walk till late in the course of the disease. The muscles of the shoulder girdle are severely affected in the advanced cases with relative sparing of the deltoid, biceps and triceps although these muscles are also weak. Ocular, pharyngeal and cardiac muscles are not involved. The CPK levels are normal or moderately elevated. The conduction velocity is normal. The EMG demonstrates the maximal changes in the tibialis anterior where abundant positive sharp waves and fibrillation potentials may be recorded. Many motor units are polyphasic and prolonged with normal amplitudes.

Atypical features found in some of the patients were marked quadriceps weakness, proximal weakness only or facial weakness. In five individuals homozygous for the common mutation and haplotype, there were no clinical symptoms including two older adults (ages 50 and 68 years).

Epidemiology:

The disease has been reported in **Palestinian Arabs from Ramallah** and **Bedouins from the Negev**.

Molecular genetics:

UDP-Nacetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene (GNE)
(chromosomal locus 9p12-13)

The same missense mutation [M712T] was found in Bedouins, Arabs and Jews and Karaites.

References:

- Argov Z, Eisenberg I, Grabov-Nardini G, Sadeh M, Wirguin I, Soffer D, Mitrani-Rosenbaum S. Hereditary inclusion body myopathy: The Middle Eastern genetic cluster. *Neurology* 2003;60:1519-1523.
- Argov Z, Yarom R. "Rimmed vacuole myopathy" sparing the quadriceps. A unique disorder in Iranian Jews. *J Neurol Sci* 1984;64:33-43.
- Eisenberg I, Avidan N, Potikha , Hochner H, Chen M, Olender M, Olender T, Barash M, Shemesh , Sadeh M, Grabov-Nardini G, Shmlevich I, Friedmann A, Karpati G, Bradley WG, Baumbach L, Lancet D Ben Asher E, Beckmann J, Argov Z, Mitrani-Rosenbaum S. The UDP-Nacetylglucosamine 2-epimerase /N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy. *Nature Genet* 2001;29:83-87.

Infantile bilateral striatal necrosis (Strionigral degeneration)

Autosomal recessive (MIM 271930)

Infantile bilateral striatal necrosis (IBSN) encompasses several syndromes of bilateral symmetric, spongy degeneration of the caudate nucleus, putamen, and globus pallidus. The clinical picture includes developmental arrest beginning at the age of 7 to 15 months, choreoathetosis, and dysphagia. Pendular nystagmus appeared at a late stage. MRI, performed at various stages of the disease, showed severe basal ganglia atrophy. Postmortem study in one patient showed severe atrophy of the lenticular nuclei with gliosis and loss of neurons. Treatment with biotin appears to arrest or improve the disease.

Epidemiology:

The disorder was reported in several members of a **Bedouin tribe from the Negev**.

Molecular genetics:

nup62 gene (chromosomal locus 19q13.32-19q13.4)

The same mutation [Q391P] was found in all the patients

References:

Straussberg R, Shorer Z, Weitz R, Basel L, Kornreich L, Corie CI, Harel L, Djaldetti R, Amir J. Familial infantile bilateral striatal necrosis: clinical features and response to biotin treatment. *Neurology* 2002;59:983-989

Basel-Vanagaite L, Muncher L, Straussberg R, Pasmanik-Chor M, Yahav M, Rainshtein L, Walsh CA, Magal N, Taub E, Drasinover V, Shalev H, Attia R, Rechavi G, Simon AJ, Shohat M. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. *Ann Neurol*. 2006;60:214-222

Infantile neuroaxonal dystrophy

Autosomal recessive (MIM 256600)

Infantile neuroaxonal dystrophy (INAD) is a neurodegenerative disease characterized by pathologic axonal swelling and spheroid bodies in the central nervous system. Onset is within the first 2 years of life with death by age 10 years.

INAD is characterized mainly by a pyramidal syndrome with spastic tetraplegia, hyperreflexia, and visual impairment. Axonal swellings and spheroids are found throughout the central nervous system including in peripheral tissues.

Epidemiology:

The disorder was reported in several members of a **Bedouin Kindred and another bedouin family from the Negev**.

Molecular genetics:

PLA2G6 gene (chromosomal locus 22q13.1)

The same mutation [V691del] was found in all the patients. In a Muslim family the mutation c.2251G>A was characterized.

References:

Khateeb S, Flusser H, Ofir R, Shelef I, Narkis G, Vardi G, Shorer Z, Levy R, Galil An, Elbedour Kl., Birk OS. PLA2G6 mutation underlies Infantile neuroaxonal dystrophy Am J Human Genet 2006;79:942-948.

Intellectual disability, progressive spastic paraplegia, shy character and short stature

Autosomal recessive (MIM 607245)

The affected children present with severe intellectual disability absent speech, microcephaly, shy character stereotypic laughter, muscular hypotonia progressing to spastic paraplegia, inability to walk.

Epidemiology:

AP4B1 gene (chromosomal locus 14q11-q12)

The disease has been reported in one Muslim Arab family from Jerusalem. The affected were homozygous for c. 478_788TAT (p.Ser739delinsVal).

References:

Abou Jamra R, Philippe O, Raas-Rothschild A, Eck SH, Graf E, Buchert R, Borck G, Ekici A, Brockschmidt FF, Nöthen MM, Munnich A, Strom TM, Reis A, Colleaux L. Adaptor protein complex 4 deficiency causes severe autosomal-recessive intellectual disability, progressive spastic paraplegia, shy character, and short stature. *Am J Hum Genet.* 2011;10;88:788-795.

Intrahepatic cholestasis, familial

Autosomal recessive (MIM 243300)

Cholestasis is the failure of bile production or bile flow into the small intestine. It may occur due to the impairment of a specific molecular process or as a secondary consequence of structural abnormality or hepatic or bile duct damage. Progressive familial intrahepatic cholestasis represents a group of inherited disorders characterized by progressive liver disease with impairment of bile flow but without structural abnormality. A large subgroup is recognized by elevation of serum bile acids with low concentration of biliary bile acid, low or normal cholesterol and normal γ GT suggesting an intrinsic defect in the bile acid transport at the hepatocyte canalicular membrane. Several patients have been reported among Arabs in the **Galilee**. The disorder was familial, with no gender predominance, the birth weight was normal and the jaundice appeared before the age of 6 months, most before the age of 3 weeks. The initial clinical examination revealed hepatomegaly with or without splenomegaly, jaundice, low body weight with laboratory data indicative of cholestasis except for GGTP which is normal at least at an early stage. The disease progress rapidly to cirrhosis and most of the children die before the age of 18 months. The liver biopsy demonstrated in some of the siblings giant cell transformation while in other paucity of intrahepatic ducts.

References:

Naveh Y, Bassan L, Rosenthal E, Berkowitz D, Jaffe M, Mandel H, Berant M. progressive familial intrahepatic cholestasis among the Arabs population in Israel. J Ped Gastroenterol Nutr 1997; 24:548-554.

Johanson-Blizzard syndrome

Autosomal recessive (MIM 243800)

Johanson-Blizzard syndrome is a disorder that includes congenital exocrine pancreatic insufficiency, multiple malformations such as nasal wing aplasia, and frequent mental retardation.

Epidemiology:

The disorder was reported in a Muslim Arab patient from the Galilee.

Molecular genetics:

UBR1 gene (chromosomal locus 15q14-21.1)

The mutation [2598delA] was found in the patient

References:

Zenker M, Mayerle J, Lerch MM, Tagariello A, Zerres K, Durie PR, Beier M, Hulskamp G, Guzman C, Rehder H, Beemer FA, Hamel B, Vanlieferinghen P, Gershoni-Baruch R, Vieira MW, Dunic M, Auslender R, Gil-da-Silva-Lopes VL, Steinlicht S, Rauh M, Shalev SA, Thiel C, Ekici AB, Winterpacht A, Kwon YT, Varshavsky A, Reis A. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). *Nat Genet.* 2005;37:1345-1350..

Joubert syndrome

Autosomal recessive (OMIM 213300)

Joubert syndrome is characterized by hindbrain malformation, hypotonia, cerebellar ataxia and developmental delay. Oculomotor apraxia and abnormalities in breathing patterns are frequent. Associated anomalies include digital signs, retinal and renal involvement.

The disease was reported in several Ashkenazi Jewish families. All the patients presented with developmental delay and the cognitive functioning was in the mildly to severely retarded range. In all the patients the nystagmus and vision improved over the first years of life. Oral motor difficulties were invariably present from birth resulting in swallowing and chewing difficulties and failure to thrive in most cases.

Epidemiology and molecular genetics

Joubert syndrome and related disorders are a heterogeneous group with at least 10 loci

TMEM21 (chromosomal locus 11p12-p13/3)

A mutation [G230C] was found in two Muslim Arab families

References

Valente EM, Logan CV, Mougou-Zerelli S, Lee JH, Silhavy JL, Brancati F, Iannicelli M, Travaglini L, Romani S, Illi B, Adams M, Szymanska K, Mazzotta A, Lee JE, Tolentino JC, Swistun D, Salpietro CD, Fede C, Gabriel S, Russ C, Cibulskis K, Sougnéz C, Hildebrandt F, Otto EA, Held S, Diplas BH, Davis EE, Mikula M, Strom CM, Ben-Zeev B, Lev D, Sagie TL, Michelson M, Yaron Y, Krause A, Boltshauser E, Elkhartoufi N, Roume J, Shalev S, Munnich A, Saunier S, Inglehearn C, Saad A, Alkindy A, Thomas S, Vekemans M, Dallapiccola B, Katsanis N, Johnson CA, Attié-Bitach T, Gleeson JG. Mutations in TMEM216 perturb ciliogenesis and cause Joubert, Meckel and related syndromes. *Nat Genet.* 2010;42:619-625.

Kohlschutter-Tonz syndrome

Autosomal recessive (MIM 226750)

The affected children seemed to develop normally until the onset of seizures at age 11 months to 4 years. Progressive mental deterioration, accompanied by muscular spasticity may follow. They have yellow teeth as a result of amelogenesis imperfecta

Epidemiology:

The disease was diagnosed in a **Druze family from the Galilee and several families in another Druze village from the Galilee.**

Molecular genetics:

ROGDI gene (*chromosomal locus 16p13.3*)

The mutation [c.469C>T (p.Arg157*)] was found all the patients from the Druze village

References:

Mory A, Dagan E, Illi B, Duquesnoy P, Mordechai S, Shahor I, Romani S, Hawash-Moustafa N, Mandel H, Valente EM, Amselem S, Gershoni-Baruch R. A nonsense mutation in the human homolog of *Drosophila* rogdi causes Kohlschutter-Tonz syndrome. *Am J Hum Genet.* 2012;90:708-714.

Zlotogora J, Fuks A, Borochowitz Z, Tal Y. Kohlschutter-Tonz syndrome: epilepsy, dementia and amelogenesis imperfecta. *Am J Med Genet* 1993;46: 453-454.

Krabbe disease

Autosomal recessive (MIM 245200)

In the classical infantile form onset is within the first 6 months of life and the course of the disease is rapidly progressive leading to death before the age of two years. The presenting symptom may be increased irritability, fever of unknown origin, regression in the motor development, later on the rigidity with opisthotonus is characteristic. At a very early stage of the disease there is very high protein concentration in the CSF without abnormal cells. The disease is caused by the lack of activity of the lysosomal enzyme beta galactocerebrosidase. The determination of the activity in leukocytes, and/or fibroblasts allow for diagnosis of the disease but is not suitable for carrier detection since there is a wide range of normal activity, with considerable overlap between normal homozygotes and carriers.

Epidemiology:

In Israel, most of the patients affected with Krabbe disease were either **Druze from a village in the north of Israel** or **Muslims Arabs either from two villages included within Jerusalem** or from **Jaffo**.

Molecular genetics:

glycosylceramidase gene GALC (chromosomal locus 14q31)

All the patients originating from the two villages in Jerusalem are homozygous for a same unique G to A transition at position 1582 [D528N] while the Druze patients are homozygous for a T to G transversion at position 1748. In a screening for [D528N] in more than 600 adults in the 2 villages, the carrier frequency was 0.07.

References:

- Rafi MA, Luzi P, Zlotogora J, Wenger DA. Two different mutations are responsible for Krabbe disease in the Druze and Moslem Arab population in Israel. *Hum Genet* 1996; 97:304-308.
- Zlotogora J, Levy-Lahad E, Legum C, Iancu TC, Zeigler M, Bach G: Krabbe disease in Israel. *Isr J Med Sci* 1991;27:196-198.

Lafora disease

Autosomal recessive (MIM 254780, 607566)

There are three types of progressive myoclonic epilepsy (PME). The Lafora type shows onset of grand mal seizures and/or myoclonus around the fifteenth year of life, rapid and severe mental deterioration, often with psychotic symptoms, short survival, histologic finding of Lafora bodies, and autosomal recessive inheritance. The two other types are the autosomal recessive Unverricht-Lundborg disease, and the dominant form of myoclonic epilepsy without inclusion bodies (Hartung type).

Epidemiology:

The disorder was reported in the Muslim Arab families (one from the Palestinian Authority).

Molecular genetics:

laforin gene (EPM2A) (chromosomal locus 6q24))

the complete deletion of exon 2 was found in all the patients

References:

Gomez-Abad C, Afawi Z, Korczyn AD, Misk A, Shalev SA, Spiegel R, Lerman-Sagie T, Lev D, Kron KL, Gómez-Garre P, Serratosa JM, Berkovic SF. Founder effect with variable age at onset in Arab families with Lafora disease and EPM2A mutation. *Epilepsia*. 2007;48:1011-1104.

Laron syndrome, Pituitary dwarfism II

Autosomal recessive (MIM 262500)

Dysfunction of GHR is characterized by clinical hyposomatotropism manifest by short stature, delayed bone age, and occasionally blue sclerae and hip degeneration. Additional features include delayed bone maturation and the absence of bone dysplasias and chronic diseases. Laron syndrome patients have low IGF1 despite normal or increased levels of GH. The GH is functionally normal by the criteria that it reacts normally with a variety of antisera and binds normally to GH receptors. IGF1 is low in GHIS, and exogenous GH does not induce an IGF1 response or restore normal growth.

Epidemiology:

The disease was reported among palestinian Arab including a Druze family.

Biochemical defect:

Failure to generate insulin-like growth factor I (IGF1) in response to growth hormone.

Molecular genetics:

Growth hormone receptor gene (chromosomal locus 5p13-p12)

In the three families described the patients were homozygous, each with a different mutation: [R217X] and [post R defect] in the Palestinian families and [785-1G>T] in the Druze family

References:

- Laron Z. Laron syndrome: the personal experience 1958-2003. J Clin Endocrinol Metab 2004; 89:1031-1044
- Laron Z, Kelijman M, Pertzalan A, Keret R, Schoffner IM, Parks JS. Human growth hormone gene deletion without antibody formation or growth arrest during treatment- a new disease entity? Isr J Med Sci 1985;21:999-1006.
- Shevah O, Borrelli P, Rubinstein M, Laron Z. Identification of two novel mutations in the human growth hormone receptor gene. J Endocrinol Invest. 2003; 26:604-608.
- Shevah O, Rubinstein M, Laron Z. Molecular defects of the growth hormone receptor gene, including a new mutation, in Laron syndrome patients in Israel : relationship between defects and ethnic groups. Isr Med Assoc J. 2004;6:630-633.
- Shevach O, Laron Z. Genetic analysis of the pedigrees and molecular defects of teh GH receptor gene in the Israeli cohort of patients with Laron Syndrome. Pediatric Endocrinology Reviews. 2006;3:489-497

Leber congenital amaurosis

Autosomal recessive (MIM 204000)

Leber congenital amaurosis is the designation for a group of autosomal recessive retinal dystrophies that represent the most common genetic causes of congenital visual impairment in infants and children. LCA is characterized by moderate to severe visual impairment identified at or within a few months of birth, infantile nystagmus, sluggish pupillary responses (and occasionally a paradoxical pupil response), and absent or poorly recordable electroretinographic responses early in life. Additional features include symmetric midfacial hypoplasia with enophthalmos and hypermetropic refractive errors. While there is substantial variation between families, intrafamilial similarities exist. Leber congenital amaurosis is an heterogeneous disorder and at least 5 loci for causative mutations have been demonstrated.

Epidemiology:

The disorder have been diagnosed in several **Muslim Arab** families and was found to be frequent in **one village in the Galilee**.

Molecular genetics:

CRB1 gene (chromosomal locus 1q31-q32.1)

In all the patients of the village a 10-bp (del 4121-4130) deletion was segregating with the disease in the 12th exon lying in the 3' end of the gene.

RDH12 gene (chromosomal locus 14q23.3)

In one Muslim family the patients were homozygous for c.377C>T

References:

- Benayoun L, Spiegel R, Auslender N, Abbasi AH, Rizel L, Hujeirat Y, Salama I, Garzozzi HJ, Allon-Shalev S, Ben-Yosef T. Genetic heterogeneity in two consanguineous families segregating early onset retinal degeneration: The pitfalls of homozygosity mapping. *Am J Med Genet A*. 2009;149A:650-656.
- Gerber S, Perrault I, Hanein S, Shalev S, Zlotogora J, Barbet F, Ducroq D, Dufier J, Munnich A, Rozet J, Kaplan J. A novel mutation disrupting the cytoplasmic domain of CRB1 in a large consanguineous family of Palestinian origin affected with Leber congenital amaurosis. *Ophthalmic Genet* 2002;23:225-235.

Lethal congenital contractural syndrome 2

Autosomal recessive (MIM 607598)

Two autosomal autosomal recessive syndromes with arthrogryposis are frequent in Bedouin tribes from the **Negev**. The phenotype described is similar to the Finnish type lethal congenital contracture syndrome yet differs by some additional craniofacial/ocular findings, by the lack of hydrops, multiple pterygia, and fractures, and by the normal duration of pregnancy. The major unique and previously undescribed clinical feature of the lethal contractural syndrome type 3 is a markedly distended urinary bladder as well as other urinary abnormalities. The vast majority of the children die shortly after birth. Prenatal diagnosis is possible as early as 15 weeks gestation by ultrasound, demonstrating fetal akinesia, limb contractures, hydramnios, and distended urinary bladder.

Molecular genetics:

ERBB3 (*Her3 gene*) (chromosomal locus 12q13)

All the patients in the tribe were homozygous for IVS10-8A>G mutation

References:

Narkis G, Ofir R, Landau D, Manor E, Volokita M, Hershkowitz R, Elbedour K, Birk OS. Lethal Contractural Syndrome Type 3 (LCCS3) Is caused by a mutation in *PIP5K1C*, which encodes PIPKI γ of the phosphatidylinositol pathway. *Am J Hum Genet* 2007; 81:530-540.

Lethal congenital contractural syndrome type 3

Autosomal recessive (OMIM 607598)

Two autosomal autosomal recessive syndromes with arthrogryposis are frequent in Bedouin tribes from the **Negev**. The phenotype of type 3 is similar to the Finnish type lethal congenital contracture syndrome yet differs by some additional craniofacial/ocular findings, by the lack of hydrops, multiple pterygia, and fractures, and by the normal duration of pregnancy. The major difference with type 2 is the absence of distended urinary bladder as well as other urinary abnormalities. The vast majority of the children die shortly after birth.

Molecular genetics

PIP5K1C gene (chromosomal location 19p13).

In the Bedouin tribe all the patients are homozygous for G757A

References

Narkis G, Ofir R, Landau D, Manor E, Volokita M, Hershkowitz R, Elbedour K, Birk OS. Lethal contractural syndrome type 3 (LCCS3) is caused by a mutation in *PIP5K1C*, which encodes PIPKI gamma of the phosphatidylinositol pathway. *Am J Hum Genet.* 2007;81:530-539

Lethal congenital contractural syndrome type 4

Autosomal recessive (OMIM 607598)

Two autosomal autosomal recessive syndromes with arthrogryposis are frequent in Bedouin tribes from the **Negev**. The phenotype of type 4 is similar to type 3 lethal congenital contracture

Molecular genetics

MYBPC1 gene (chromosomal location 12q23).

In two families from different tribes the patients were homozygous for c.952C>T (p.R318*)

References

Markus B, Nerkis G, Landau D, Birk ZE, Cohen I, Birk OS. Autosomal recessive lethal contractural syndrome (LCCS4) caused by a mutation in MYBPC. Hum Mutation 2012;33:1435-1438.

Leukocyte adhesion deficiency, type II, Rambam Hasharon syndrome. Congenital disorder of glycosylation IIc (CGD IIc)

Autosomal recessive (MIM 266265)

In 2 unrelated Arab Moslem boys, each born of a consanguineous mating, a distinctive syndrome was described comprising unusual facial appearance, severe mental retardation, microcephaly, cortical atrophy, seizures, hypotonia, dwarfism.

Both had had recurrent episodes of bacterial infection, mainly pneumonia, periodontitis, otitis media, and localized cellulitis without the formation of pus. Infections were associated with a high leukocyte count and a marked defect in neutrophil mobility was observed.

The Bombay blood phenotype is typically caused by the presence in the homozygous state of a recessive gene (hh) resulting in a deficiency in the synthesis of the red cell H antigen, a fucosylated carbohydrate.

Epidemiology:

The disorder has been reported in two unrelated Arab families in Israel.

Molecular genetics:

GDP fucose transporter gene

Homozygosity for [T308R] was found in two Israeli Arab patients.

References:

Etzioni A, Frydman M, Pollack S, Avidor I, Phillips ML, Paulson JC, Gershoni-Baruch R. Recurrent severe infections caused by a novel leukocyte adhesion deficiency. *New Eng J Med* 1992;327:1789-1792.

Frydman M, Etzioni A, Eidlitz-Markus T, Avidor I, Varsano I, Shechter Y, Orlin JB, Gershoni-Baruch R. Rambam-Hasharon syndrome of psychomotor retardation, short stature, defective neutrophil motility, and Bombay phenotype. *Am J Med Genet* 1992; 44: 297-302.

Lubke T, Marquardt T, Etzioni A, Hartmann E, von Figura K, Korner C.

Complementation cloning identifies CGD-IIc a new type of congenital disorders of glycosylation, as a GDP-fucose transporter deficiency. *Nature Genet* 2001;28:73-76.

Leukodystrophy autosomal recessive

Autosomal recessive (MIM)

The phenotype included convulsions near birth, mental retardation and cerebral palsy. Brain MRI demonstrated significant reduction in white matter and agenesis of corpus callosum.

Molecular genetics and epidemiology

DHCR24 gene (chromosome locus 1p33-1p32.3)

The syndrome was diagnosed in several patients from An Israeli-Bedouin kindred from the Negev. In all the patients a homozygous mutation C307T was characterized.

References

Zolotushko J, Flusser H, Markus B, Heverin M, Björkhem I, Sivan S, Birk OS. Characterization of the genetic defect underlying an autosomal recessive leukodystrophy. ASHG congress 2010

Leukodystrophy with Spastic Paraparesis and Dystonia

Autosomal recessive (MIM 611026)

The patients, have normal early development and present at 4–6 years of age with gait disturbance due to lower-limb spasticity. At this age the disease was rapidly progressive and the patients required walking aids at 7 years. When they were 7–12 years of age, their spasticity extended to the upper limbs. Dystonia was evident from a few years of onset, involving trunk, limbs, and face and interfering with articulation and swallowing. Upper-motor-neuron involvement with positive Babinski sign became evident toward 10 years of age in the patients. The patients' cognitive abilities, normal at 6 years of age with acquisition of reading and writing skills at a normal pace, deteriorated with age. At 12–14 years of age, these patients were no longer able to read or write; this deterioration was not attributed to the motor disability or the dysarthria. Cerebellar dysfunction with dysmetria and dysdiadochokinesis were additionally noted. At mid adolescence, the patients lost ambulation.

Molecular genetics and epidemiology

FA2H gene (chromosome 16q23)

The syndrome was diagnosed in several patients from two Muslim Arab families in Jerusalem. In all these patients a homozygous intronic mutation, c.7861G/A was characterized.

References

Edvardson S, Hama H, Shaag A, Gomori JM, Berger I, Soffer D, Korman SH, Taustein I, Saada A, Elpeleg O. Mutations in the fatty acid 2-hydroxylase gene are associated with leukodystrophy with spastic paraparesis and dystonia. *Am J Hum Genet* 2008;83:643–648.

Limb defects, distal transverse, with mental retardation and spasticity.

Autosomal recessive (MIM 246555)

Jancar reported the case of a 19-year-old man with ectrodactyly, mental retardation, and spastic paraplegia. The same combination was later found in two other Arab families in Israel.

References:

Zlotogora J. Mental retardation, spasticity and transverse limb defects. *Am J Med Genet* 1987;26: 221-223.

Zlotogora J, Glick B. Jancar syndrome: mental retardation, spasticity, and distal transverse limbs defects. *J Med Genet* 1993;47: 89-90.

Limb girdle muscular dystrophy LGMD2B

Autosomal recessive (MIM 253601)

Within a large **Muslim Arab kindred** two different type of muscular dystrophy were found: one with a congenital onset and another with a typical form of limb girdle muscular dystrophy.

Most of the patients with the limb girdle muscular dystrophy presented with distal lower muscular weakness in the second half of the third decade as gait difficulties.

Epidemiology:

The syndrome has been reported in a single large Muslim Arab kindred from a town in **Vadi Ara**.

Molecular genetics:

Dysferlin (chromosomal locus 2p13) (MIM 603009).

All the patients from the kindred affected with the LGMD are homozygotes for a 23 bp insertion which has result from tandem replication probably as a result from replication slippage. This mutation is predicted to introduce a premature termination of the protein 41 AA downstream. This mutation was not found in the patients with the congenital disease confirming that it represents indeed a different disorder.

References:

- Bashir R, Britton S, Strachan T, Keers S, Vafiadaki E, Lako M, Richard I, Marchand S, Bourg N, Argov Z, Sadeh M, Mahjneh I, Marconi G, Passos-Bueno MR, Moreira, Zatz EM, Beckmann JS, BushbyK. A gene related to *Caenorhabditis elegans* spermatogenesis factor fer-1 is mutated in limb-girdle muscular dystrophy type 2. *Nature Genetics* 1998; 20:37-42.
- Mahjneh I, Vannelli G, Bushby K, Marconi GP. A large inbred Palestinian family with two forms of muscular dystrophy. *Neuromusc disord* 1992;2:277-283.

Limb girdle muscular dystrophy LGMD2C

Autosomal recessive (MIM 253700)

Limb-girdle muscular dystrophies (LGMD) represent a group of diseases characterized mainly by muscle wasting of the upper and lower limbs, with a wide range of clinical severity. The clinical heterogeneity is paralleled by molecular heterogeneity; each of the ten forms of autosomal recessive LGMD recognized to date is caused by mutations in a distinct gene.

Epidemiology:

Several affected individuals from a Bedouin tribe living in a village in the **North of Israel**, were homozygous for [525delT].

Molecular genetics :

gamma-sarcoglycan gene (SGCG e (chromosomal locus 13q12).

All the affected individuals from the Bedouin tribe were homozygous for [525delT].

References:

Goldberg Y, Harel T, Chervinski I, Ofir R, Birk OS, Shalev SA. A third locus of Limb Girdle Muscular Dystrophy (LGMD) among Arabs in the north of Israel: LGMD2C in a large consanguineous Bedouin family. Meeting ASHG 2004.

Limb girdle muscular dystrophy LGMD2I

Autosomal recessive (MIM 607155)

Limb-girdle muscular dystrophies (LGMD) represent a group of diseases characterized mainly by muscle wasting of the upper and lower limbs, with a wide range of clinical severity. The clinical heterogeneity is paralleled by molecular heterogeneity; each of the ten forms of autosomal recessive LGMD recognized to date is caused by mutations in a distinct gene. In a large consanguineous Bedouin tribe living in northern Israel, the disease was diagnosed in 15 individuals. The most consistent findings were severe involvement of the proximal muscles as compared to the distal muscles, and severe involvement of the lower limbs relative to the upper limbs. Seemingly, the age of onset in the patients studied was independent of the pace of progression. However, a correlation was noted between the severity of limb weakness and respiratory involvement: patients confined to wheelchairs were those affected by restrictive lung disease.

Molecular genetics and Epidemiology:

Fukutin-related protein FKRP gene (chromosomal locus 19q13.3).

LGMD2I is due to mutations in the FKRP gene, which is also defective in congenital muscular dystrophy MDC1C

All the affected individuals from the Bedouin tribe living in a village in the **North of Israel**, were homozygous for [R54W].

References:

Harel T, Goldberg Y, Shalev SA, Chervinski I, Ofir R, Birk OS. Limb-girdle muscular dystrophy 2I: phenotypic variability within a large consanguineous Bedouin family associated with a novel FKRP mutation. *Eur J Hum Genet.* 2004;12:38-43.

Lipoid proteinosis

Autosomal recessive (MIM 247100)

The association of early hoarseness with an unusual skin eruption suggests this diagnosis. Cutaneous and mucosal infiltrations may take protean forms. Most of the cases were reported on an ad hoc basis by dermatologists or laryngologists. Papular infiltration of the margin of the lids producing 'itchy eyes,' and infiltration in the tongue and its frenulum, in the larynx leading to hoarseness, and in the skin (e.g., elbows and axilla) are characteristic. Bilateral intracranial calcifications are found in at least 70% of cases.

Epidemiology:

5 affected individuals in a Bedouin family.

Molecular genetics:

Extracellular matrix protein 1 gene ECM gene (chromosomal locus 1q21)

All the patients were homozygous for a splice mutation in the intron 3' flank of exon 8.

References:

Birnbaum R, Zvulunov Fuchs AL, Ofir R, Cohen AD, Elbedour K, Agami O, Birk OS. Lipoid proteinosis: Clinical heterogeneity in an extended Bedouin family with a novel splice-site mutation in the ECM1 gene. ASHG meeting 2004.

MACS syndrome (macrocephaly, alopecia, cutis laxa, and scoliosis)

Autosomal recessive (MIM)

The association of macrocephaly, alopecia, cutis laxa and scoliosis was reported in three patients with a single kindred.

Epidemiology:

3 affected individuals in a Muslim Arab family.

Molecular genetics:

RIN2 gene (chromosomal locus 20p11.21-p11.23)

A homozygous frameshift mutation was characterized in the patients c.1731delC

References:

Basel-Vanagaite L, Sarig O, HersHKovitz D, Fuchs-Telem D, Rapaport D, Gat A, Isman G, Shirazi I, Shohat M, Enk CD, Birk E, Kohlhase J, Matysiak-Scholze U, Maya I, Knopf C, Peffekoven A, Hennies HC, Bergman R, Horowitz M, Ishida-Yamamoto A, Sprecher E. RIN2 deficiency results in macrocephaly, alopecia, cutis laxa, and scoliosis: MACS syndrome. Am J Hum Genet. 2009;85:254-263.

Mal de Meleda (MDM) or keratosis palmoplantaris transgrediens of Siemens

Autosomal recessive (MIM 248300)

Mal de Meleda is an autosomal recessive skin disorder characterized by diffuse palmoplantar keratoderma (PPK) and transgressive keratosis with an onset in early infancy. Congenital symmetrical cornification of the palms and soles, with ichthyotic changes elsewhere, characterizes this disorder which derives its name from its relatively high frequency among inhabitants of the Island of Meleda, Dalmatia, Yugoslavia. Hyperhidrosis, perioral erythema, and lichenoid plaques were also noted. There is no associated involvement of other organs; however, a spectrum of clinical presentations with optional and variable features has been described.

Epidemiology:

The disease is found in a large **Muslim Arab** kindred from a town in the **region of Vadi Araa**.

Molecular genetics:

Secreted LY6/UPAR-related protein 1 gene (SLURP1) (chromosomal locus 8q24-qter).

In the large Palestinian Israeli pedigree, patients are homozygous for a new mutation that substitutes an arginine for a conserved glycine residue at position 86 G86R.

References:

Eckl KM, Stevens HP, Lestringant GG, Westenberger-Treumann M, Traupe H, Hinz B, Frossard PM, Stadler R, Leigh IM, Nurnberg P, Reis A, Hennies HC. Mal de Meleda (MDM) caused by mutations in the gene for SLURP-1 in patients from Germany, Turkey, Palestine, and the United Arab Emirates. *Hum Genet* 2003;112:50-56.

Mammary digital nail syndrome

Autosomal dominant

In a large family from a Druze village in the North of Israel several individuals affected with a rare syndrome including breast hypertrophy in affected females and onychodystrophy/anonychia with anomalies of the distal phalanges

Molecular genetics:

Unknown

The gene has been mapped to 22q12.3-13.1

References:

Genzer-Nir M, Khayat M, Kogan L, Cohen HI, Hershkowitz M, Geiger D, Falik-Zaccai TC. Mammary-digital-nail (MDN) syndrome: a novel phenotype maps to human chromosome 22q12.3-13.1. *Eur J Hum Genet.* 2010;18:662-667..

Mannosidosis, alpha

Autosomal recessive (MIM 248500)

Two siblings with mild mental retardation, delayed speech, a suggestion of coarse or full facies, and limited mobility of the large joints have been reported in a family from **Gaza**.

Molecular genetics:

Alpha mannosidase gene (chromosomal locus 19centq12)

A 212A→T transversion in the MANB gene, resulting in a his71-to-leu amino acid substitution was found in the siblings.

References:

Bach G, Kohn G, Lasch EE, Massri ME, Ornoy A, Sekeles E, Legum C, Cohen MM. A new variant of mannosidosis with increased residual enzymatic activity and mild clinical manifestation. *Pediat Res* 1978; 12:1010-1015.

Nilssen O, Berg T, Riise HM, Ramachandran U, Evjen G, Hansen GM, Malm D, Tranebjaerg L, Tollersrud OK. alpha-Mannosidosis: functional cloning of the lysosomal alpha-mannosidase cDNA and identification of a mutation in two affected siblings. *Hum Mol Genet* 1997;6:717-726.

Maple syrup urine disease

Autosomal recessive (MIM 248600)

The features of maple syrup urine disease (MUSD) are mental and physical retardation, feeding problems, and a maple syrup odor to the urine (alpha-keto-beta-methylvaleric acid). The clinical phenotypes may differ by presentation and severity. The most severe is the classical manifesting in the newborn period and result in severe neurologic manifestations and if not treated may lead to death.

Epidemiology:

The disease has been diagnosed in several villages in the **Galilee** (Muslim Arab and Druze) and among Bedouins from the Galilee (Mandel H) and in a tribe from the **Negev**. The estimated incidence of MSUD is 1/40,000 live births among non-Jews in Israel.

Molecular genetics:

MSUD is caused either by a defect in the E1-alpha subunit of branched-chain keto acid dehydrogenase, a defect in the E1-beta subunit (248611) is referred to as type IB, a defect in the E2 subunit (248610); or a defect in the E3 subunit..

The nonsense mutation [E1- R242X] was found in the bedouin kindred from the Negev. Several other mutations have been reported in the North of Israel: [E1- S289L- β] mutation characterized in a Druze kindred and [E2- S133stop] in another Druze family from another village. The mutation [E2- H391R] in a Bedouin tribe; [E1- C29W α] in a christian family and [V69G β] in a Muslim Arab family.

References:

- Chinsky J, Appel M, Almashanu S, Costeas P, Ambulos N Jr, Carmi R. A nonsense mutation (R242X) in the branched-chain alpha-keto acid dehydrogenase E1alpha subunit gene (BCKDHA) as a cause of maple syrup urine disease. *Mutations in brief* no. 160. Online. *Hum Mutat.* 1998;12:136.
- Potashnik R, Carmi R, Sofer S, Bashan N, Abeliovich D. Maple syrup disease in a Bedouin tribe, pre and postnatal diagnosis. *Isr J Med Sci* 1987 23:886-889.
- Chuang JL, Wynn RM, Moss CC, Song JL, Li J, Awad N, Mandel H, Chuang DT. Structural and biochemical basis for novel mutations in homozygous israeli maple syrup urine disease patients a proposed mechanism for thiamin-responsive phenotype. *J Biol Chem.* 2004; 279:17792-17800.
- Wynn RM, Chuang JL, Sansaricq C, Mandel H, Chuang DT. Biochemical basis of type IB (E1{beta}) mutations in maple syrup urine disease. A prevalent allele in patients from the Druze kindred in Israel. *J Biol Chem* 2001; 276: 36550-36556.

Meckel syndrome

Autosomal recessive (MIM 249000)

Meckel syndrome classically includes encephalocele, polydactyly and polycystic renal disease leading to severe oligohydramnion, Potter sequence and early death because of pulmonary hypoplasia. The clinical picture is variable even within families and the most constant features seems to be a renal anomaly.

Epidemiology:

The syndrome is frequent among Arabs in Israel and probably in all the Middle East.

Molecular genetics:

MKS1 gene (chromosomal locus 17q22-23)

One Muslim Arab family with [Q350X]

MKS3 gene (chromosomal locus 8q24)

One Muslim Arab family c.1065+1delG in an other family c.IVS10+1delG

RPGRIP1L (chromosomal locus 16q12.2)

The mutation Gln40X was characterized in one Bedouin family

CC2D2A (chromosomal locus 4p15.32)

One Muslim Arab family with c.3084delG

TMEM231 (chromosomal locus 16q23.1)

One Muslim Arab family with c.644+4A>G

CEP290 (chromosomal locus 12q21.32)

One Muslim Arab family with c.1225delA

References:

Khaddour R, Smith U, Baala L, Martinovic J, Clavering D, Shaffiq R, Ozilou C, et al.. Spectrum of MKS1 and MKS3 Mutations in Meckel Syndrome: A Genotype-Phenotype Correlation. Human Mutation, Mutation in Brief # 960 (2007) Online
Zlotogora J. Genetic disorders among the Palestinian Arabs. 2: neural tube defects and hydrocephalus. Am J Med Genet 1997;71:33-35.

Meconium ileus, familial

Autosomal recessive (MIM)

Meconium ileus is a form of neonatal intra-luminal intestinal obstruction that occurs in the terminal ileum due to accumulation of thick, viscid meconium. Meconium ileus occurs in ~15-20% of CF patients. Eighty to ninety percent of infants presenting with Meconium ileus will develop CF later in life. A unique autosomal recessive form of non-CF meconium ileus was shown to be prevalent in a large inbred Israeli-Bedouin kindred. Some of the patients required surgical treatment while others managed with conservative treatment. The penetrance of the mutation was incomplete. Homozygosity of affected individuals at the locus of CFTR and at the CF modifier 1 locus was ruled out.

Molecular genetics and epidemiology

GUCY2C (chromosome locus 12p13)

The syndrome was diagnosed in several patients from an Israeli-Bedouin kindred from the Negev . In all the patients a homozygous missense mutation was characterized c. 1160A>G (p.Asp387Gly). Of 240 unrelated Israeli-Bedouin control individuals, three were heterozygous for the affected allele and none were homozygous for the mutation. A second homozygous mutation in the same gene, c.2270dupA was found in another case of non-CF MI in another inbred Bedouin kindred.

References

Romi H, Cohen I, Landau D, El-Krinawi S, Yerushalmi B, HersHKovitz R, Newman-Heiman N, Cutting GR, Ofir R, Sivan S, Birk O S. Meconium Ileus Caused by Mutations in GUCY2C, Encoding the CFTR-Activating Guanylate Cyclase 2C . Am J Hum Genet 2012;90:89389-9

Medium chain acyl CoA dehydrogenase deficiency MCAD

Autosomal recessive (MIM 201450)

A newborn infant died suddenly on the second day of life. A previous sibling had also died in similar circumstances aged 3 weeks. Urine organic acid and bloods pot acylcarnitine analysis were consistent with MCADD.

In one Muslim Arab family originating from the region of Jerusalem.

Epidemiology and Molecular genetics:

ACADM gene (*chromosomal locus 1p31*).

Several patients were reported among Muslims (IVS3-1G>C, 362C>T) and Bedouins (c.415-419 del GATCA; del621 AGTA)

References:

Korman SH, Gutman A, Brooks R, Sinnathamby T, Gregersen N, Andresen BS. Homozygosity for a severe novel medium-chain acyl-CoA dehydrogenase (MCAD) mutation IVS3-1G > C that leads to introduction of a premature termination codon by complete missplicing of the MCAD mRNA and is associated with phenotypic diversity ranging from sudden neonatal death to asymptomatic status. *Mol Genet Metab.* 2004; 82:121-129.

Mental retardation, non syndromic

Autosomal recessive (MIM 608443)

Epidemiology:

In several Muslim Arab families originating from a small village on the Mediterranean coast non syndromic mental retardation was diagnosed.

Molecular genetics:

CC2d1A gene (chromosomal locus 19p13.12-p13.2).

All the patients were homozygous for G408fsX437 leading to a deletion causing the removal of aa 408-547

References:

Basel-Vanagaite L, Attia R, Yahav M., Ferland R, Anteki L, Walsh CA, Olender T, Straussberg R, Maga N, Taub E, Drasinover V, Alkelai A, Bercovich D, Rechavi G, Simon AJ, Shohat M. The CC2D1A, a member of a new gene family with C2 domains, is involved in autosomal recessive non syndromic mental retardation . J Med Genet. 2006; 43:203-210.

Mental retardation anterior maxillary protrusion, and strabismus (MRAMS),

Autosomal recessive (MIM 613671)

Epidemiology:

In a single family a syndrome characterized by severe mental retardation, anterior maxillary protrusion, and strabismus was reported. Six of 7 sibs had anterior maxillary protrusion with vertical maxillary excess, open bite, and prominent crowded teeth. The patient with mental retardation but without a jaw anomaly was somewhat less severely retarded and developed seizures and severe psychosis in adolescence. None of the unaffected sibs with normal intelligence had jaw or dental anomalies. Routine laboratory studies, brain MRI, and cytogenetic studies were all normal.

Molecular genetics:

SOBP gene (chromosomal locus 6q21).

All the patients were homozygous for R551X.

References:

Basel-Vanagaite L, Rainshtein L, Inbar D, Gothelf D, Hennekam R, Straussberg R. Autosomal recessive mental retardation syndrome with anterior maxillary protrusion and strabismus: MRAMS syndrome. *Am. J. Med. Genet.* 143A: 1687-1691, 2007.

Birk E, Har-Zahav A, Manzini C M, Pasmanik-Chor M, Kornreich L, Walsh C A, Noben-Trauth K, Albin A, Simon AJ, Colleaux L, Morad Y, Rainshtein L et al. SOBP is mutated in syndromic and nonsyndromic intellectual disability and is highly expressed in the brain limbic system. *Am. J. Hum. Genet* 2010;87:694-700.

Mental retardation with post natal microcephaly

Autosomal recessive (MIM 611966)

Epidemiology:

In one Muslim Arab family originating from a large Arab town in Israel non syndromic mental retardation was diagnosed in three sisters. They were affected with intellectual disability of various degree and developed during the years microcephaly. There were no dysmorphic features, autistic features or epilepsy at the time that the girls were reported (eldest was 8 years old).

Molecular genetics:

TRAPPC9 gene (chromosomal locus 8q).

All the patients were homozygous for c.1423C>T [p.R377X].

References:

Mochida GH, Mahajnah M, Hill AD, Basel-Vanagaite L, Gleason D, Hill RS, Bodell A, Crosier M, Straussberg R, Walsh CA. A truncating mutation of TRAPPC9 is associated with autosomal-recessive intellectual disability and postnatal microcephaly. *Am J Hum Genet.* 2009;85:897-902.

Metachromatic leukodystrophy, late infantile

Autosomal recessive (MIM 250100)

Metachromatic leukodystrophy is a lysosomal storage disease in which the deficiency of the hydrolase aryl sulfatase A leads to a progressive degenerative disease of the nervous system. In the late infantile type the affected child's psychomotor development is normal up to the age of one year. The first symptom is a stagnation in the motor development; many of the affected children are late to walk alone or do not achieve this stage.

Afterward there is a progressive deterioration first of the motor functions and later of the mental abilities. Involvement of the peripheral nervous system lead to the absence of the tendon reflexes as well as a prolonged nerve conduction in the electromyogram and an elevation of the protein content of the cerebrospinal fluid. In most cases the child get to a vegetative stage at the age 3-5 and dies soon afterward.

Epidemiology:

The disease is relatively frequent among Arabs in particular in the **region of Jerusalem** (1/20,000) and in the **Galilee**

Molecular genetics:

Arylsulfatase A gene ARASA (chromosomal locus 22q13.31 qter).

All the patients from the region of Jerusalem either Muslim Arab or Christian were homozygous for a single mutation [459+1 G→A], which is the most frequent mutation causing late infantile MLD in Europe. It has been assumed that the mutation was introduced to the region from Europe at the time of the Crusades. In the Galilee, 5 different new mutations have been found among patients who originated from 7 different villages very close one to the other. In each of the village a single mutation was found and the patients were always homozygote for the mutation. Among Christians Arabs the mutations [Q190H] was found in one village and [T274M] in two villages, and among Muslim Arabs [G86D] in one village, [R370W] in another village and [S96L] in two other villages.

References:

Heinisch U, Zlotogora J, Kafert S, Gieselmann V. Multiple mutations are responsible for the high frequency of metachromatic leukodystrophy in a small geographic area. *Am J Hum Genet* 1995;56:51-57.

Zlotogora J, Furman-Shaharabani Y, Harris A, Barth ML, von Figura K, Gieselmann V: A single origin for the most common mutation causing late infantile metachromatic leukodystrophy *J Med Genet* 1994;31:672-674.

Zlotogora J, Gieselmann V, von Figura K, Zeigler M, Bach G. Late infantile metachromatic leukodystrophy in Israel. *Biomed Pharmacother* 1994;48:347-350.

3-Hydroxy-3-Methyl Glutaric aciduria

Autosomal recessive (MIM 246450)

This rare disorder affects ketogenesis and L leucine catabolism, appears generally after the first year of life after fasting and its clinical features include vomiting, seizures metabolic acidosis hypoglycemia and lethargy. These symptoms sometimes progress to coma with fatal outcome in approximately 20% of the cases.

Epidemiology:

Two Palestinian patients were reported

Molecular genetics:

HMGCL gene is localized to 1p36.1-p35.

Two mutations were found in homozygosity in the patients [p.C174Y], [p.D42G].

References:

Menao S, López-Viñas E, Mir C, Puisac B, Gratacós E, Arnedo M, Carrasco P, Moreno S, Ramos M, Gil MC, Pié A, Ribes A, Pérez-Cerda C, Ugarte M, Clayton PT, Korman SH, Serra D, Asins G, Ramos FJ, Gómez-Puertas P, Hegardt FG, Casals N, Pié J. Ten novel HMGCL mutations in 24 patients of different origin with 3-hydroxy-3-methylglutaric aciduria. Hum Mutat. 2009;30:E520-29

Methyl malonic aciduria due to methylmalonic CoA mutase deficiency

Autosomal recessive (MIM 251000)

In the severe form the child presents with profound metabolic acidosis, developmental retardation, and an unusual biochemical triad: methylmalonicaciduria, long chain ketonuria, and intermittent hyperglycinemia. Valine, isoleucine, or high protein intake accentuated the biochemical abnormalities.

Some of the patients respond to vitamin B12 administration. Thus, in some but not all patients, the characteristic and potentially lethal episodes of ketoacidosis can be avoided. Among those patients not responsive to B12, some have hyperglycinemia and some do not.

There are at least 4 forms of methylmalonicaciduria: that in which production of both adenosylcobalamin and methylcobalamin is deficient so that methylmalonicaciduria and homocystinuria coexist that due to deficiency of the mutase apoenzyme (a form which is always vitamin B12-unresponsive), and 2 forms with deficiency of adenosylcobalamin (either of which may be B12 responsive or unresponsive).

Patients with the mut-zero defect present earlier in infancy than do other patients and die during the first few months of life. In response to cobalamin supplements, marked decreases in the concentration of methylmalonic acid in blood or urine occurred in most cbl A patients and in nearly half the cbl B patients, but not in mut-zero or mut- patients.

Epidemiology:

Several patients were reported from the Palestinian territories, one family was from a large Arab town in Israel.

Molecular genetics:

methylmalonic CoA mutase gene is localized to 6p21.

Three mutations were found in the patients, all in homozygosity: [IVS3+3A→G], [N219Y] and [E414X].

References:

Berger I, Shaag A, Anikser A, Baumgartner ER, Bar-Meir M, Joseph A, Elpeleg O. Mutation analysis of the MCM gene in Israeli patients with mut⁰ disease. Mol Genet Metabol 2001;73:107-110.

Microcephaly

Autosomal recessive

In a large Israeli Arab family 9 children with congenital microcephaly severe mental retardation spasticity and hypereflexia.

Molecular genetics:

The syndrome has been mapped to 12q24

References:

Drasinover V, Shalev S, Marom D, Rechavi G, Amariglio N, Shohat T, Shohat M, Magal N. Linkage analysis using GeneChip Microarray maps new locus for microcephaly to chromosome 12q24. Meeting ASHG 2004.

Microcephaly intellectual disability and dysmorphism

Autosomal recessive

Six individuals of consanguineous inbred Israeli Bedouin kindred presented with severe congenital microcephaly, intellectual disability, hypertonia at birth that lessened with age, and dysmorphism: hirsutism, low anterior hairline and bitemporal narrowing, low-set posterior rotated protruding ears, strabismus and fleshy slightly protruding lower lip, slightly anteverted nares with a normal philtrum; eyebrows were arched and thick with sparse hair in their medial segment and there was lateral puffiness above the upper eyelids and a skin fold partially covering the inferior eyelids, as well as long eyelashes. All were born at term with birth weights adequate for gestational age but with head circumference below third percentile all at birth and throughout follow-up. Weight and height were between less than third percentile and up to tenth percentile. All patients had different levels of ataxia, evident as early as 18 months of age. Intellectual disability was severe. Cerebellar signs were evident on neurological exam: uncoordinated hand movements were seen, and the only patient who walked independently had severe ataxia.

Molecular genetics:

FRMD4A (gene location 10p)

All the patients were homozygous for c.2134_2146dup13 (p.Gly716Profs*25)

References:

Fine D, Flusser H, Markus B, Shorer Z, Gradstein L, Khateeb S, Langer Y, Narkis G, Birk R, Galil A, Shelef I, Birk OS. A syndrome of congenital microcephaly, intellectual disability and dysmorphism with a homozygous mutation in *FRMD4A*. *Eur J Hum Genet.* 2014 Nov 12. [Epub ahead of print]

Microcephaly early onset intractable seizures and developmental delay

Autosomal recessive (MIM)

The affected children present with microcephaly, infantile onset seizures developmental delay and variable behavioral problem particularly hyperactivity.

Epidemiology and molecular genetics:

Polynucleotide kinase 3' phosphatase PNKP. (chromosomal locus 19q13.33)

The syndrome has been reported in three unrelated Palestinian Arab families, from Jordan and the US. All the affected children were homozygous for the same mutation G975A (p.E326K)

References:

Shen J, Gilmore EC, Marshall CA, Haddadin M, Reynolds JJ, Eyaid W, Bodell A, Barry B, Gleason D, Allen K, Ganesh VS, Chang BS, Grix A, Hill RS, Topcu M, Caldecott KW, Barkovich AJ, Walsh CA. Mutations in PNKP cause microcephaly, seizures and defects in DNA repair. *Nat Genet.* 2010;42:245-249.

Microcephaly with spastic quadriplegia

Autosomal recessive (MIM 251280)

Several families have been reported in Arabs living in Israel. The patients present with marked microcephaly, intractable seizures, quadriplegia and profound mental retardation. The seizures were in rule of the myoclonic type with an early onset.

Epidemiology:

The syndrome have been reported in several unrelated families

Molecular genetics:

Unknown

References:

- Frydman M, Jager-Roman E, de Vries L, Stoltenburg-Didinger G, Nussinovitch M, Sirota L. Alpers progressive infantile neuronal poliodystrophy: an acute neonatal form with findings of the fetal akinesia syndrome. *Am J Med Genet* 1993; 47:31-36.
- Gross-Tsur V, Joseph A, Blinder G, Amir N. Familial microcephaly with severe neurological deficits: a description of five affected siblings. *Clin Genet* 1995 47:33-37
- Straussberg R, Kornreich L, Harel L, Varsano I. Autosomal recessive microcephaly with neonatal myoclonic seizures: clinical and MRI findings. *Am J Med Genet* 1998; 80:136-139.

Microcephaly, neuronal degeneration, and neonatal death

Autosomal recessive (MIM)

The affected children presented with severe microcephaly (head circumference 9 standard deviations below mean) and death by 1 year. MRI at 3 months of age revealed extreme microcephaly with as severely simplified gyral pattern. The cerebral cortex was even more notably smaller than the skull, with subarachnoid fluid separating the two, an indication of secondary shrinkage of the brain usually reflecting degeneration

Epidemiology:

The syndrome have been reported in a large consanguineous Muslim Arab pedigree from the central region of Israel

Molecular genetics:

ZNF335 gene (chromosomal location 20q13.12)

A c.3332g>a mutation results in a predicted change of Arg R (CGC) at amino acid position 1111 of the protein was observed in all the patients

References:

Yang YJ, Baltus AE, Mathew RS, Murphy EA, Evrony GD, Gonzalez DM, Wang EP, Marshall-Walker CA, Barry BJ, Murn J, Tatarakis A, Mahajan MA, Samuels HH, Shi Y, Golden JA, Mahajnah M, Shenhav R, Walsh CA. Microcephaly Gene Links Trithorax and REST/NRSF to Control Neural Stem Cell Proliferation and Differentiation. *Cell*. 2012;151:1097-1112.

Microcephalic osteodysplastic primordial dwarfism type II

Autosomal recessive (MIM 210720)

The children have severe intrauterine growth retardation (IUGR) and severe postnatal growth retardation; relatively proportionate head size at birth which progresses to true and disproportionate microcephaly; progressive disproportion of the short stature secondary to shortening of the distal and middle segments of the limbs; a progressive bony dysplasia with metaphyseal changes in the limbs; epiphyseal delay; progressive loose jointedness with occasional dislocation or subluxation of the knees, radial heads, and hips; unusual facial features including a prominent nose, eyes that appear prominent in infancy and early childhood, ears that are proportionate, mildly dysplastic, and usually missing the lobule; a high squeaky voice; abnormally small, and often dysplastic or missing, dentition; a pleasant, outgoing, sociable personality; and autosomal recessive inheritance. Farsightedness, scoliosis, unusual pigmentation, and truncal obesity often develop with time. Some individuals seem to have increased susceptibility to infections. A number of affected individuals had developed dilation of the CNS arteries variously described as aneurysms and moyamoya disease.

There is variability between affected individuals even within the same family.

Epidemiology and molecular genetics:

PCNT gene (chromosomal locus 21q22.3)

The mutation p.R994fsX1053 was reported in one Palestinian patient

References:

Rauch A, Thiel CT, Schindler D, Wick U, Crow YJ, Ekici AB, van Essen AJ, Goecke TO, Al-Gazali L, Chrzanowska KH, Zweier C, Brunner HG, Becker K, Curry CJ, Dallapiccola B, Devriendt K, Dörfler A, Kinning E, Megarbane A, Meinecke P, Semple RK, Spranger S, Toutain A, Trembath RC, Voß E, Wilson L, Hennekam R, de Zegher F, Dörr HG, Reis A. Mutations in the Pericentrin (PCNT) Gene Cause Primordial Dwarfism. *Science*. 2008;319:816-819.

Microphthalmia/anophthalmia

Autosomal recessive (MIM 251600)

Microphthalmia/anophthalmia is a clinically heterogeneous disorder of eye formation ranging from small size of a single eye to the complete absence of ocular tissues. Several families have been reported with a recessive inheritance. The disorder is characterized by variability among individuals, even among sibs - from uni to bilateral and mild coloboma to anophthalmia. There are no other malformations and the affected patients are mentally normal.

Epidemiology:

The disorder was reported in several Arab families

Molecular genetics:

CHX10 gene (chromosomal locus 14q32)

A mutation A227T was reported in one Arab kindred and a deletion of exon 3 in other large kindred from Gaza..

References:

- Bar-Yosef U, Abuelaish I, Harel T, Hendler N, Ofir R, Birk OS. CHX10 mutations cause non-syndromic microphthalmia/anophthalmia in Arab and Jewish kindreds. Hum Genet. 2004;115:302-309. Jul 15 [Epub ahead of print]
- Porges Y, Gershoni-Baruch R, Leibur R, Goldscher D, Zonis S, Shapira I, Miller B. Hereditary microphthalmia with colobomatous cyst. Am J Ophthalmol 1992 114:30-34.

Mitochondrial Hsp60 Chaperonopathy disease

Autosomal recessive (MIM 118190)

The disease was diagnosed in many children of a large Bedouin family. Early clinical manifestations in all patients included hypotonia, nystagmus, and psychomotor developmental delay, followed by appearance of prominent spasticity, developmental arrest, and regression. Head circumference, which was normal at birth, showed decreased growth rate. Seizures were reported and feeding problems commonly led to malnutrition and growth failure. Death usually occurred within the first two decades of life from aspiration pneumonia or sudden death of unknown cause. One of the most extreme presentations was hydrops fetalis in one patient, who eventually died at the age of 2 years. Patients with the more severe course died before the age of 2 years, with some of them never gaining social eye contact or any other developmental milestone. These severely affected patients suffered from recurrent episodes of shallow breathing and apneic spells during acute febrile illnesses and died during such episodes.

In patients who survived beyond the age of 2 years, the motor disability, which mainly included progressive limb spasticity and contractures, seemed to be more prominent than the psycho intellectual impairment.

All patients exhibited a thin corpus callosum and showed various degrees of ventricular enlargement. Enlargement of sulci and subarachnoid spaces, mainly in the frontal and parietal areas, were observed many of the patients. The degree of widening of cerebral sulci was in concordance with the severity of the clinical symptoms. The brain stem was thin in all patients. In many patients, the cerebellum and vermis were smaller than normal for age.

Epidemiology and Molecular genetics:

HSPD1 (chromosomal locus 1q41-q42)

In a large highly consanguineous Israeli Bedouin kindred residing in several adjacent villages of the Galilee region of northern Israel several patients were diagnosed. All those examined were homozygous missense mutation g.1512A/G in exon 2 at position 86 of the cDNA sequence [D29G].

References:

Magen D, Georgopoulos C, Bross P, Ang D, Segev Y, Goldsher D, Nemirovski A, Shahar E, Ravid S, Luder A, Heno B, Gershoni-Baruch R, Skorecki K, Mandel H. Mitochondrial hsp60 chaperonopathy causes an autosomal-recessive neurodegenerative disorder linked to brain hypomyelination and leukodystrophy. *Am J Hum Genet.* 2008; 83:30-42.

Mitochondrial depletion syndrome

Autosomal recessive (MIM 251880)

Mitochondrial disease that does not involve qualitative errors in mtDNA but rather quantitative depletion of mtDNA in affected tissues. In this disorder, individuals exhibit variable levels of mtDNA depletion (up to 98%) in affected tissues, while unaffected tissues have relatively normal levels of mtDNA.

Hepatocerebral form

Most patients presented soon after birth with muscle weakness and hepatic failure or renal tubulopathy associated with a severe depletion of mtDNA (88 to 99%) in affected tissues at postmortem. These infants usually died before 9 months of age. A milder variant had been described in some patients, with a slowly progressive mitochondrial encephalomyopathy starting in childhood and associated with less severe depletion of mtDNA in skeletal muscle (66 to 86%).

Individuals with the hepatocerebral form of mitochondrial DNA depletion syndrome have early progressive liver failure and neurologic abnormalities, hypoglycemia, and increased lactate in body fluids. Affected tissues show both decreased activity of the mtDNA-encoded respiratory chain complexes (I, III, IV, and V) and mtDNA depletion.

Myopathic disease.

The disease was reported in four patients, three of them Muslim Arabs. The patients were normal in the first 6 months of life and then developed a severe myopathy and progressively lost spontaneous activity. The patients did not suffer from any involvement of other organs.

Epidemiology and Molecular genetics:

mitochondrial deoxyguanosine kinase DGUOK (chromosomal locus 2p13)

mitochondrial thymidine kinase TK2 (s 16q22)

succinate CoA ligase ADP forming beta subunit SUCLA2 (13q12.2-q13)

Hepatocerebral form. In a large Druze kindred a same DGUOK single nucleotide deletion 204delA causing a frameshift mutation at codon 68 was found in all the patients.

Encephalomyopathy: One Muslim Arab pedigree the patients were homozygous for a mutation in SUCLA2 32720del43ins5.

Myopathy: several Muslim Arab patients were homozygous I181A] in the TK2 gene.

References:

Elpeleg O, Miller C, HersHKovitz E, Bitner-Glindzicz M, Bondi-Rubinstein G, Rahman S, Pagnamenta A, Eshhar S, Saada A. Deficiency of the ADP-forming succinyl-CoA synthase activity is associated with encephalomyopathy and mitochondrial DNA depletion. *Am J Hum Genet.* 2005;76:1081-1086

Mandel H, Szargel R, Labay V Elpeleg O, Saada A, Shalata A, Anbinder Y, Berkowitz D, Hartman C, Barak M, Eriksson S, Cohen N: The deoxyguanosine kinase gene is mutated in individuals with depleted hepatocerebral mitochondrial DNA. *Nature Genet.* 2001; 29:337-341.

Saada A; Shaag A, Mandel H, Nevo Y, Eriksson S, Elpeleg O : Mutant mitochondrial thymidine kinase in mitochondrial DNA depletion myopathy. *Nature Genet* 2001; 29:342-324.

Mitochondrial disease due to a defective mitochondrial translation.

Autosomal recessive (MIM 609204)

A single patient was reported with agenesis of corpus callosum, dysmorphism SGA, low set ears, non pitting edema brachydactyly and redundant skin over the neck. Neonatal lactic acidosis was fatal with markedly decreased complex I and IV activity in muscle and liver and a generalized mitochondrial translation defect identified in pulse-label experiments.

Epidemiology:

One bedouin family from the Negev

Molecular genetics:

Mitochondrial ribosomal protein 16 MRPS16 gene (chromosomal locus 10q22.1)

The patient was homozygous for Arg111Ter.

References:

Miller C, Saada A, Shaul N, Shabtai N, Ben-Shalom E, Shaag A, HersHKovitz E, Elpeleg O. Defective mitochondrial translation caused by a ribosomal protein (MRPS16) mutation. *Ann Neurol* 2004;56:734-738

Mitochondrial encephalopathy with cytochrome C oxydase deficiency

Autosomal recessive (MIM 606965)

Two siblings were reported with developmental delay, hemiplegia, convulsions asymmetrical brain atrophy and low cytochrome c oxydase activity in skeletal muscle.

Epidemiology:

One bedouin family from the the center

Molecular genetics:

KIAA0971 gene(chromosomal locus 2q31-q36)

The patients were homozygous for c.1246C>T.

References:

Ghezzi D, Saada A, D'Adamo P, Fernandez-Vizarra E, Gasparini P, Tiranti V, Elpeleg O, Zeviani M. FASTKD2 Nonsense Mutation in an Infantile Mitochondrial Encephalomyopathy Associated with Cytochrome C Oxidase Deficiency. Am J Hum Genet. 2008;83:415-423.

Monilethrix

Autosomal dominant (MIM 158000)

Monilethrix is a rare disorder characterized by hair fragility and hyperkeratotic papules.

Epidemiology:

The syndrome has been reported in several families.

Molecular genetics:

Keratin hair basic 6, KHb6 (chromosomal locus 12q13)

In a large pedigree from the **region of Jerusalem**, 3 siblings were severely affected with complete lack of scalp hair since the age of 2 months with no improvement with age and with keratotic lesions over the scalp and large body areas. The affected patients carried a mutation in hHb6 G→A leading to Glu413Lys and the three severely affected siblings were homozygotes for the mutation. The mutation has been reported in another independent pedigree with the disorder.

In another three-generation pedigree from a single Muslim Arab kindred, 23 affected individuals were reported carrier of a mutation in hHb6 [E410D].

References:

- Horev L, Glaser B, Metzker A, Ben-Amitai D, Vardi D, Zlotogorski A. Monilethrix: mutational hotspot in the helix termination motif of the human hair basic protein keratin 6. *Hum Hered* 2000;50:325-330.
- Oetting W, Fryer JP, Wyman Z, Shtorch A, Cordoba M, Lazarov A, Reish O. Molecular analysis of an extended Palestinian family from Israel with monilethrix. *Genet in Medicine* 1999;1:109-111.
- Zlotogorski A, Horev L, Glaser B. Monilethrix: a keratin hHb6 mutation is co dominant with variable expression. *Exp Dermatol* 1998;7:268-272.

Molybdenum cofactor deficiency

Autosomal recessive (MIM 252150)

The disorder manifest shortly after birth with profound neurological abnormalities in particular neonatal seizures unresponsive to any therapy, abnormal tone, opisthotonus. Craniofacial dysmorphic features include narrow bifrontal diameter, and enophthalmos, ectopia lentis and neurological deterioration. No treatment has been successful in halting or reversing the neurological damages and the development of mental retardation. Molybdenum cofactor biosynthesis proceeds in three steps (1) conversion of GPT to a stable precursor Z, (2) conversion of precursor Z to MPT and (3) insertion of molybdenum into MTP forming molybdenum cofactor. Molybdenum cofactor deficiency defines two complementation groups type A and B and it was assumed that the complementation group A patients are defective in the early step of molybdenum cofactor synthesis leading to precursor Z. This was confirmed by the identification of the gene MOCS1 which encodes for the two enzymes necessary for the precursor Z formation. The MOCS1 gene maps to chromosome 6p and account for 70% of the molybdenum cofactor deficiency cases. The second gene MOCS2 encodes for the MTP synthase and mutations in this gene cause molybdenum cofactor deficiency of type B.

Epidemiology:

The disease was found in Muslim Arab families from **several villages in the Galilee.**

Molecular genetics:

Molybdenum cofactor synthesis-1 MOCS1 (6p21.3)

Different mutations are responsible for the high frequency of the disorder in Israel: [1bpdel, 722T], [R39L], [R91W].

References:

Reiss J, Cohen N, Dorche C, Mandel H, Mendell RR et al.. Mutations in a polystronic nuclear gene associated with Molybdenum cofactor deficiency. Nat Genet 1998;20:51-53.

Mucopolidosis II

Autosomal recessive (MIM 252500)

This is a Hurler-like condition with severe clinical and radiologic features, peculiar fibroblast inclusions, and no excessive mucopolysacchariduria. Congenital dislocation of the hip, thoracic deformities, hernia, and hyperplastic gums are evident soon after birth. Retarded psychomotor development, clear corneas, and restricted joint mobility are other features. It is also known as I-cell disease (for 'inclusion cell disease').

Epidemiology:

The disease has been diagnosed in several Muslim Arab families in Israel.

Molecular genetics:

Alpha/beta subunit of the phosphotransferase gene (Chromosomal locus 12q23.3)

Two mutations c3502-3delCT and IVS 18+1 G>A were each found in several Muslim Arab families. Other mutations were C3613 C>T, C2916 insT

References:

- Bargal R, Zeigler M, Abu-Libdeh B, Zuri V, Mandel H, Ben Neria Z, Stewart F, Nursel E, Hindi T, Merrer ML, Bach G, Raas-Rothschild A. When Mucopolidosis III meets Mucopolidosis II: GNPTA gene mutations in 24 patients. *Mol Genet Metab.* 2006;88:359-363.
- Tiede S, Storch S, Lubke T, Henrissat B, Bargal R, Raas-Rothschild A, Bräulke T. Mucopolidosis II is caused by mutations in GNPTA encoding the alpha/beta GlcNAc-1-phosphotransferase. *Nat Med.* 2005;11:1109-112.

Mucopolidosis III

Autosomal recessive (MIM 252600)

The first symptom of the disorder is a mild limitation of the small articulations of the fingers, which may allow for an early clinical diagnosis in children at risk. The disease is progressive leading progressively to large joint limitation and physical handicap. The facial features become progressively coarse. Usually there is no or little mental impairment.

The lysosomal enzymes cannot reach the lysosome since they do not have the mannose 6 phosphate necessary for them to be recognized by the receptor. While the enzymes are absent from the lysosome they are present in huge quantities in the serum.

The disease is caused by a deficiency of the enzyme N acetylglucosaminidase 1 phosphotransferase. In the type IIIC the enzyme retains its activity on synthetic substrates but lacks activity on lysosomal enzymes.

Epidemiology:

The disease has been diagnosed in several families (Druze and Muslim Arab) in **several villages in the Galilee**. The disorder is particularly frequent in one **Druze** village in the upper Galilee.

Molecular genetics:

Gamma subunit of the phosphotransferase gene(Chromosomal locus 4q21-23).

Alpha/beta subunit of the phosphotransferase gene(Chromosomal locus 12q23.3)

Several different mutations exist among the Arabs in Israel. The mutation 500insC was found among Druze and Muslim Arabs, the mutation c.3503_delTC among Muslim Arabs and the mutation G106S in Druze only.

References:

Raas-Rothschild A, Cormier-Daire V, Bao M, Genin E, Salomon R, Brewer K, Zeigler M, Mandel H, Toth S, Roe B, Munnich A, Canfield WM. Molecular basis of variant pseudo-Hurler polydystrophy (Mucopolidosis III). *J Clin Invest* 2000; 1105:573-681.
 Raas-Rothschild A, Bargal R, Goldman O, Ben-Asher E, Groener JE, Toutain A, Stemmer E, Ben-Neriah Z, Flusser H, Beemer FA, Penttinen M, Olender T, Rein AJ, Bach G, Zeigler M. Genomic organisation of the UDP-N-acetylglucosamine-1-phosphotransferase gamma subunit (GNPTAG) and its mutations in mucopolidosis III. *J Med Genet.* 2004; 41:e52.

Mucopolipidosis IV.

Autosomal recessive (MIM 252650)

The disorder is characterized by psychomotor retardation and ophthalmological abnormalities including, corneal opacities, retinal degeneration, strabismus and often myopia. Psychomotor retardation is usually evident before the first year of life and the maximal developmental level of the patients is around 12 to 15 months in motor functions and language. Some patients show slight improvement during the first decade in both mental and motor functions. Usually there is no obvious deterioration of the clinical signs at least during the first two decades of life.

Epidemiology

The disease was diagnosed in two **Druze** families from the Golan Heights each from a different village.

Molecular genetics

MCOLN1 gene (Chromosomal locus 19p13.2-13.3).

The mutation in one Druze family was [R322X] and [R403C] in the other.

References:

Bargal R, Avidan N, Ben-Asher E, Olender Z, Zeigler M, Frumkin A, Raas-Rothschild A, Glusman G, Lancet D, Bach G. Identification of the gene causing mucopolipidosis IV. Nat Genet 2001; 26:118-121.

Multiple congenital anomalies hypotonia seizures syndrome

Autosomal recessive (MIM)

The disorder is characterised by dysmorphic features and multiple congenital anomalies together with severe neurological impairment, chorea and seizures leading to early death.

Epidemiology

The disease was diagnosed in 4 families from a single Muslim kindred **from the Galilee**

Molecular genetics

PIGN gene (chromosomal locus 18q21.32-q22.1).

All the affected were homozygous for c.2126G>A (p.Arg709Gln).

References:

Maydan G, Noyman I, Har-Zahav A, Ben Neriah Z, Pasmanik-Chor M, Yeheskel A, Albin-Kaplanski A, Maya I, Magal N, Birk E, Simon AJ, Halevy A, Rechavi G, Shohat M, Straussberg R, Basel-Vanagaite L. Multiple congenital anomalies-hypotonia-seizures syndrome is caused by a mutation in PIGN. J Med Genet. 2011;48:383-389

Multiple pterygium syndrome

Autosomal recessive (MIM 265000)

Clinical features included short stature; pterygia of the neck, axilla, and antecubital, popliteal, digital, and intercrural areas; multiple joint contractures with crouched stance and cleft palate. Males had small penis and scrotum and cryptorchidism; females had aplasia of the labia majora and small clitoris. Skeletal anomalies included fusion of cervical vertebrae, scoliosis, flexion contraction of fingers, and 'rocker-bottom' feet with vertical talus.

Epidemiology

The disorder has been reported to be relatively frequent among Arabs. Two of the families reported in Kuwait were Palestinian

Molecular genetics

Unknown

References:

Teebi AS, Daoud AS. Multiple pterygium syndrome: a relatively common disorder among Arabs. *J Med Genet* 1990;27:791.

Myasthenia gravis, congenital

Autosomal recessive (MIM 603034)

The disorder is heterogenous. Most of the patients present at birth however some present later in childhood. The presenting symptoms include feeding difficulties, respiratory distress, ptosis and weakness. The most common features are ptosis, muscular weakness, restrictive ventilatory defects, dysphagia. Most of the children have a severe kyphoscoliosis. A low pupillary reaction to light is seen in the patients.

Molecular genetics:

COLQ (chromosomal locus 3p24).

The mutation [G240X was found in several Arab patients from the region of Jerusalem.

CHRNE chromosomal locus 3p24).

The mutation [c.163T>C, p.W55R] was found in a family of Muslim origin from the region of Jerusalem. The patients presented a severe form of the disease

References:

Shapira YA, Sadeh ME, Bergtraum MP, Tsujino A, Ohno K, Shen XM, Brengman J, Edwardson S, Mathot I, Engel AG. Three novel COLQ mutations and variation of phenotype expressivity due to G240X. *Neurology* 2002;58:603-609.

Shen XM, Brengman JM, Edwardson S, Sine SM, Engel AG. Highly fatal fast-channel syndrome caused by AChR ϵ subunit mutation at the agonist binding site. *Neurology*. 2012;79:449-454

Myasthenia limb girdle syndrome

Autosomal recessive (MIM 254300)

Within a large Muslim Arab kindred two different type of muscular dystrophy were found: one with a congenital onset and another with a typical form of limb girdle muscular dystrophy.

All the patients with the congenital form of muscular dystrophy had generalized muscular weakness and hypotonia at birth without arthrogryposis. The clinical course was relatively benign with stabilisation of the clinical picture at different ages and at variable degrees of severity. The pattern of muscle weakness and wasting was more marked in the proximal upper limb-girdle and trunk muscles. Lower limb muscles were more mildly involved. Serum CK was normal or moderately increased. All patients had normal intelligence.

Following the molecular diagnosis six patients were re-examined and presented permanent limb-girdle weakness, with episodic crises without clear precipitating factors. Following the revised diagnosis, patients were treated with salbutamol for 8 months with significant improvement in their muscle strength and function

Epidemiology:

The syndrome has been reported in a single large Muslim Arab kindred from a town in Vadi Ara.

Molecular genetics:

DOK7 (chromosomal location 4p16.3)

All the patients were homozygous for c.957delC

References:

- Mahjneh I, Bushby K, Anderson L, Muntoni F, Tolvanen-Mahjneh H, Bashir R, Pizzi A, Brockington M, Marconi G. Merosin-positive congenital muscular dystrophy: a large inbred family. *Neuropediatrics* 1999; 30:22-28.
- Mahjneh I, Lochmüller H, Muntoni F, Abicht A. DOK7 limb-girdle myasthenic syndrome mimicking congenital muscular dystrophy. *Neuromuscul Disord.* 2013;23:36-42. 2012
- Mahjneh I, Vannelli G, Bushby K, Marconi GP. A large inbred Palestinian family with two forms of muscular dystrophy. *Neuromusc disord* 1992;2:277-283.

Mycobacteriosis, atypical disseminated

Autosomal recessive (MIM 209950)

In this rare syndrome the patients are predisposed to infectious diseases caused by poorly virulent mycobacteria such as BCG vaccine, environmental mycobacteria and poorly virulent salmonella strains. The patients are healthy and seldom suffer from unusually severe bacterial, viral, fungal or parasitic disease.

Epidemiology

A patient was reported among Bedouins from the Negev.

Molecular genetics

The disorder can be caused by defects in the genes encoding interferon-gamma receptor-1 (IFNGR1) on chromosome 6q23-q24, interferon-gamma receptor-2 (IFNGR2) on 21q22, the beta-1 chain of the interleukin-12 receptor (IL12RB1) on 19p13, and signal transducer and activator of transcription-1 (STAT1) on 2q32. Disseminated infection with BCG and *Salmonella enteritidis* has been associated with isolated deficiency of interleukin-12B (IL12B; 161561).

The patient was homozygous for a large in frame deletion of 12165 nucleotides in IL12RB1.

References

Fieschi C, Bosticardo M, de Beaucoudrey L, Boisson-Dupuis S, Feinberg J, Santos OF, Bustamante J, Levy J, Candotti F, Casanova JL. A novel form of complete IL-12/IL-23 receptor beta1 deficiency with cell surface-expressed nonfunctional receptors. *Blood*. 2004; 104:2095-2101.

Myoclonic epilepsy, Unverricht-Lundborg

Autosomal recessive (OMIM 254800)

The first signs of the disease begin at the age of 6-13 years with convulsions. Myoclonus usually appears the year later predominantly in the extremities. The disease is characterized by a severe stimulus sensitive myoclonic and generalized seizures as well as neurologic deterioration including dementia and ataxia.

Epidemiology

Several patients were diagnosed in two large Arab pedigrees from different villages in the Galilee.

Molecular genetics

Cystatin B gene CSTB (chromosomal locus 21q22.3)

In one pedigree all the Arab patients from the Galilee, homozygosity for an expansion mutation was characterized.

Locus on chromosome 12

In the other pedigree all the Arab patients from the Galilee, homozygosity for a locus in the pericentric region of chromosome 12.

References

Berkovic SF, Mazarib A, Walid S, Neufeld MY, Manelis J, Nevo Y, Korczyn AD, Yin J, Xiong L, Pandolfo M, Mulley JC, Wallace RH. A new clinical and molecular form of Unverricht-Lundborg disease localized by homozygosity mapping. *Brain*. 2005;128:652-658

Mazarib A, Xiong L, Neufeld MY, Birnbaum M, Korczyn AD, Pandolfo M, Berkovic SF, Unverricht-Lundborg disease in a five generation arab family. *Neurology* 2001;57:1050-1054.

Myoglobinuria, acute recurrent

Autosomal recessive (MIM 550500)

Recurrent attacks of rhabdomyolysis with muscle pain and weakness are followed by excretion of myoglobin in the urine and occasionally acute renal failure

Epidemiology:

The syndrome has been reported in a Muslim Arab **family**

Molecular genetics:

LPIN1 gene (*chromosomal locus 2p21*).

Mutations in the LPIN1 gene cause recurrent rhabdomyolysis in childhood, and a carrier state may predispose for statin-induced myopathy. The patient was homozygous for [c.643G>T].

References:

Zeharia A, Shaag A, Houtkooper RH, Hindi T, de Lonlay P, Erez G, Hubert L, Saada A, de Keyzer Y, Eshel G, Vaz FM, Pines O, Elpeleg O. Mutations in LPIN1 Cause Recurrent Acute Myoglobinuria in Childhood. *Am J Hum Genet.* 2008; 83:489-494.

Myotonia congenita

Autosomal dominant (MIM 160800)

Autosomal myotonia congenita is a nondystrophic skeletal muscle disorder characterized by muscle stiffness and an inability of the muscle to relax after voluntary contraction. Most patients have symptom onset in the legs, which later progresses to the arms, neck, and facial muscles. Many patients show marked hypertrophy of the lower limb muscles. Some patients show transient muscle weakness

Epidemiology:

The syndrome has been reported in a single large Bedouin kindred from a village in the Galilee.

Molecular genetics:

the gene encoding skeletal muscle chloride channel-1 CLCN1 gene (chromosomal locus 7q35).

The mutation in the kindred is [G190S].

References:

Shalata A. Myotonia Congenita in a large consanguineous Bedouin- Muslim family; A unique clinical presentation and identification of a novel mutation in the (CLCN1) Chloride Channel gene. ASHG Meeting 2005.

Myopia, autosomal recessive syndrome with

Autosomal recessive

In a large Bedouin kindred from the Negev several affected individuals were reported with high myopia present from early childhood. Most affected members had high axial myopia from -5 to -18 diopters, many developed cataracts and were operated in the first second decade of life. Some of the patients had vitreal degeneration

Molecular genetics:

LEPREL1 gene encoding prolyl 3-hydroxylase 2 (chromosomal locus 3).

The mutation in the kindred is [p.Gly508Val c.1523G>T].

References:

Mordechai S, Gradstein L, Pasanen A, Ofir R, El Amour K, Levy J, Belfair N, Lifshitz T, Joshua S, Narkis G, Elbedour K, Myllyharju J, Birk OS. High Myopia Caused by a Mutation in LEPREL1, Encoding Prolyl 3-Hydroxylase 2. *Am J Hum Genet.* 2011;89:438-445.

Nail patella like renal disease

Autosomal recessive (MIM 256020)

In a family of first cousin parents of Palestinian Arabic ancestry 3 children had proteinuria and renal impairment from an early age. Two of the sibs died at ages 6 and 7 years of end-stage renal disease. Renal biopsy in the proband showed the histopathologic electron microscopic changes of the nail-patella syndrome. However, none of the family had bone or nail changes of this disorder. An autosomal recessive nephropathy or glomerulodysplasia was suggested.

Epidemiology:

The syndrome has been reported in a single family

Molecular genetics:

Unknown

References:

Salcedo JR An autosomal recessive disorder with glomerular basement membrane abnormalities similar to those seen in the nail patella syndrome: report of a kindred. Am. J Med Genet 1984; 19:579-584.

Neonatal myoclonic epilepsy

Autosomal recessive (MIM 609304)

In a family of first cousin parents of Palestinian Arabs from Jerusalem 4 siblings were affected with intractable seizures of myoclonic type and hypotonia.

Epidemiology:

The disease has been reported in a single family

Molecular genetics:

SLC25A22 gene (chromosomal locus 11p15).

The patients were homozygotes for P206L.

References:

Molinari F, Raas-Rothschild A, Rio M, Fiermonte G, Encha-Razavi F, Palmieri L, Palmieri F, Ben-Neriah Z, Kadhon N, Vekemans M, Attié-Bitach T, Munnich A, Rustin P, and Colleaux L. Impaired Mitochondrial Glutamate Transport in Autosomal Recessive Neonatal Myoclonic Epilepsy. *Am J Hum Genet* 2005;76:334-339.

Neutropenia, congenital severe

Autosomal recessive (MIM 610738)

Infantile agranulocytosis was first clearly delineated by Kostmann complete agranulocytosis developed in 3 weeks after an interval during which the patient had normal or even increased neutrophil levels, due possibly to meningitis. In addition to persistent severe absolute neutropenia (500 neutrophils per microliter or fewer) and bone marrow morphology that suggests maturational arrest of neutrophil precursors at the promyelocyte stage, variable degrees of monocytosis, eosinophilia, hypergammaglobulinemia, and thrombocytosis may be found.

Epidemiology:

In an Arab family a male and female sib with first-cousin parents with severe congenital neutropenia. The female suffered from omphalitis due to enterobacter at age 2 weeks and subsequently died from sepsis at age 1 month. The male was admitted at age 2 months with an abscess in the right inguinal region due to *Pseudomonas aeruginosa*. He suffered from frequent severe pyogenic infections

Molecular genetics:

G6PC3 (chromosomal locus 17q21.31)

The disorder was reported in several Bedouin families c.785G>A

ELA2 (chromosomal locus 19p13.3)

Several Muslim families with mutation in ELA2: c.597+5G>A (altered splicing), c.468G>C (Trp156Cys and T156C)

References:

Koren A, Bar Sela P, Barak Y, Jammalieh J, Katzuni E : Congenital dysgranulopoietic neutropenia in two siblings: clinical, ultrastructural and in vitro bone marrow culture studies. *Pediat Hemat Oncol* 1989;6:293-305.

Neutropenia, congenital severe with infantile osteoporosis

Autosomal recessive (MIM 202700)

Two children were reported presing with severe neutropenia at birth with bone marrow maturation arrest of neutrophils at the promyelocyte-myelocyte level. Gradually anemia and thrombocytopenia developed. In both children multiple fractures were noted due to severe osteoporosis.

Epidemiology:

Reported in two closely related families

Molecular genetics:

Not known

References:

Elhasid R, Hofbauer LC, Ish-Shalom S, Ben-Arush M, Koc O, Rowe JM, Etzioni A. Familial severe congenital neutropenia associated with infantile osteoporosis: a new entity. *Am J Hematol.* 2003;72:34-37.

Nephronophthisis infantile

Autosomal recessive (MIM 602088)

Ten affected subjects have been diagnosed in 6 families from a large **Bedouin kindred from the Negev**. In these patients, the manifestations ranged from a prenatal onset with maternal oligohydramnion and postnatal death because of pulmonary hypoplasia to postnatal onset before the age of 30 months. Prospective renal sonograms revealed enlarged and echogenic kidneys prior the development of symptoms and abnormal laboratory findings. The patients develop anemia, hyperkalemic metabolic acidosis and increased serum creatinine. The patients were initially with a normal arterial tension and the hypertension developed concomitantly to the renal failure. All the patient reached an end stage renal failure and progression to death was rapid. None of the patients had polyuria, polydipsia or associated ocular or hepatic complications.

Epidemiology:

The syndrome has been reported in a single **Bedouin tribe**.

Molecular genetics:

Inversin (INVS) (chromosomal locus 9q21-31).

The patients from the Bedouin tribe are homozygotes for R907X.

References.

- Haider NB, Carmi R, Shalev H, Sheffield VC, Landau D. A Bedouin kindred with infantile nephrophthisis demonstrate linkage to chromosome 9 by homozygosity mapping. *Am J Hum Genet* 1998;63:1404-1410.
- E A Otto, B Schermer, T Obara, J F O'Toole, K S Hiller, A M Mueller, R G Ruf, J Hoefele, F Beekmann, D Landau, J W Foreman, J A Goodship, T Strachan, A Kispert, M T Wolf, M F Gagnadoux, H Nivet, C Antignac, G Walz, I A Drummond, T Benzing, F Hildebrandt. Mutations in *INVS* encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. *Nat Genet.* 2003; 34:413-420.

Nephronophthisis juvenile

Autosomal recessive (MIM 256100)

The major clinical features include anemia, polyuria, polydipsia, isothermia and progressive uremia leading to early death. Hypertension and proteinuria are absent. Symmetrical destruction of the kidneys involves both tubules and glomeruli. The hallmarks of familial nephronophthisis are tubular basement membrane disruption, interstitial lymphohistiocytic cell infiltration and development cysts at the corticomedullary border of the kidneys. In later stages NPH always merges into a chronic sclerosing tubointerstitial nephropathy.

Epidemiology:

The disorder has been diagnosed in some 20 Arab families but no particular geographic distribution is evident (Frishberg Y).

Nephrotic syndromecongenital, Finnish type

Autosomal recessive (MIM 256300)

The disorder starts early in fetal life allowing for antenatal diagnosis by measuring levels of alpha fetoprotein either in the maternal serum or the amniotic fluid. The course of the disease is severe and steroid or cytotoxic drugs are without benefit and intensive medical therapy to control bacterial infections combined with renal transplantation may offer an opportunity for an acceptable quality of life.

Epidemiology:

The disease has been diagnosed in several Muslim Arab families from the **region of Jerusalem** and in the **Galilee**.

Molecular genetics:

NPHS gene *nephrin* (chromosomal locus 19q13)

In the village near Jerusalem three different mutations were found, two are frequent [Q380X], [2160insC]. The third mutation [C1707G] was recently introduced from a carrier from Jerusalem. Several other mutations were reported among Muslim Arabs.

References:

Frishberg Y, Ben-Neriah Z, Suvanto M, Rinat C, Männikkö M, Feinstein S, Becker-Cohen R, Jalanko H, Zlotogora J, Kestilä M. Misleading findings of homozygosity mapping resulting from three novel mutations in NPHS1 encoding nephrin in a highly inbred community. *Genet Med.* 2007;9:180-184.

Nephrotic syndrome steroid resistant

Autosomal recessive (MIM 600995)

The idiopathic nephrotic syndrome is a clinical pathologic entity occurring mainly in children and is characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, edema, and minimal glomerular changes. In contrast to 2 types of hereditary nephrotic syndrome, congenital nephrosis of the Finnish type and diffuse mesangial sclerosis, idiopathic nephrotic syndrome was generally regarded as a sporadic disease although a few familial cases had been reported. Most patients with idiopathic nephrotic syndrome respond to steroid therapy and show a favorable outcome. However, 20% are steroid-resistant, with progression to end-stage renal failure in many cases. Steroid-resistant idiopathic nephrotic syndrome is characterized by familial occurrence, age of onset in early childhood, resistance to steroid therapy, progression to end-stage renal disease within a few years, and absence of recurrence after renal transplantation. Two loci have been delineated both in the region 1q25-q31. SRN1 and SRN2

In the nephrotic syndrome with diffuse mesangial sclerosis, the clinical picture is characterized by the onset of asymptomatic proteinuria with subsequent steroid resistant nephrotic syndrome in infancy, and progression to renal failure and death before the age of three years. In most cases prenatal diagnosis is not possible because since alpha fetoprotein levels are normal. In one case, ultrasound showed enlarged hyperechogenic kidneys from the 14th week onwards, and the amniotic fluid level was increased to the upper normal limit.

Epidemiology:

The syndrome has been reported in several families and seems to be relatively frequent. Familial steroid resistant nephrotic syndrome has been diagnosed in several Arab families from the region of **Jerusalem and Hebron** (Frishberg Y).

Molecular genetics:

NPHS2 gene Podocin (chromosomal locus 1q25-q31)

All the patients were homzygous for the same mutation R138X.

References:

- Frishberg Y, Rinat C, Megged O, Shapira E, Feinstein S, Raas-Rothschild A. Mutations in NPHS2 encoding podocin are a prevalent cause of steroid resistant nephrotic syndrome among Israeli Arab children. *J Am Societ Nephrol* 2002; 13:400-405.
- Mendelsohn HB, Krauss M, Berant M, Lichtig C. Familial early-onset nephrotic syndrome: diffuse mesangial sclerosis. Clinico-pathological study of a kindred. *Acta Paediatr Scand* 1982;71:753-758.

Nephrotic syndrome variant

Autosomal recessive (MIM 608414)

Nephrotic syndrome is a clinical pathologic entity characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, edema, and minimal glomerular changes. In this form of the syndrome a response to steroid was reported in several families

Epidemiology:

The syndrome has been reported in an Arab family

Molecular genetics:

PLCE1 gene *Podocin* (chromosomal locus 10q23.33)

The patients were homzygous for the same mutation R493X.

References:

Hinkes B, Wiggins RC, Gbadegesin R, Vlangos CN, Seelow D, Nurnberg G, Garg P, Verma R, Chaib H, Hoskins BE, Ashraf S, Becker C, Hennies HC, Goyal M, Wharram BL, Schachter AD, Mudumana S, Drummond I, Kerjaschki D, Waldherr R, Dietrich A, Ozaltin F, Bakkaloglu A, Cleper R, Basel-Vanagaite L, Pohl M, Griebel M, Tsygin AN, Soylu A, Muller D, Sorli CS, Bunney TD, Katan M, Liu J, Attanasio M, O'toole JF, Hasselbacher K, Mucha B, Otto EA, Airik R, Kispert A, Kelley GG, Smrcka AV, Gudermann T, Holzman LB, Nurnberg P, Hildebrandt F. Positional cloning uncovers mutations in *PLCE1* responsible for a nephrotic syndrome variant that may be reversible. *Nat Genet.* 2006;38:1397-1405.

Nephrotic syndrome steroid resistant with deafness

Autosomal recessive

The idiopathic nephrotic syndrome is a clinical pathologic entity occurring mainly in children and is characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, edema, and minimal glomerular changes. Steroid-resistant idiopathic nephrotic syndrome with deafness was described in a family of palestinian origin with onset between 0.3 and 6.4 years. The histopathology diagnosis was FSGS. All the affected had congenital sensorineural deafness.

Epidemiology and Molecular genetics:

The syndrome has been reported in a family of palestinian origin. In the family the gene was mapped to 14q24.

References:

Ruf RG, Wolf MT, Hennies HC, Lucke B, Zinn C, Varnholt V, Lichtenberger A, Pasch A, Imm A, Briese S, Lennert T, Fuchshuber A, Nurnberg P, Hildebrandt F. A gene locus for steroid-resistant nephrotic syndrome with deafness maps to chromosome 14q24.2. *J Am Soc Nephrol.* 2003;14:1519-1522.

Neuropathy and bilateral striatal necrosis

Autosomal recessive (MIM606521)

The syndrome has been reported in a Bedouin Muslim family from the Galilee. Four patients, aged 7-20 years, suffered from recurrent episodes of flaccid paralysis and encephalopathy associated with bilateral striatal necrosis and chronic progressive polyneuropathy.

Molecular genetics:

SLC25A19 gene (chromosomal locus 17q25.3)

The patients were homozygous for the same mutation c. 373G>A.

References:

Spiegel R, Shaag A, Edvardson S, Mandel H, Stepensky P, Shalev SA, Horovitz Y, Pines O, Elpeleg O. SLC25A19 mutation as a cause of neuropathy and bilateral striatal necrosis. *Ann Neurol.* 2009;66:419-424.

Nevo syndrome

Autosomal recessive (MIM 601451)

In an inbred family 2 sibs and their cousin had increased growth, kyphosis, prominent forehead, volar edema, spindle-shaped fingers, wrist drop, talipes, hyperbilirubinemia, and generalized hypotonia. The authors considered their cases to be an autosomal recessive variant of Sotos syndrome but later it was proposed that these patients had a separate entity.

Two other male cases from unrelated Arab families were reported by Al Gazali et al. with similar features but without hyperbilirubinemia. Both had delayed motor development. Cognitive function was normal in one at 2 years 10 months of age.

Epidemiology:

The syndrome seems to be rare.

Molecular genetics:

Unknown

References:

- Al-Gazali LI, Bakalinova D, Varady E, Scorer J, Nork M. Further delineation of Nevo syndrome. *J Med Genet* 1997;34:366-370.
- Nevo S, Zeltzer M, Benderly A, Levy J. Evidence for autosomal recessive inheritance in cerebral gigantism. *J Med Genet* 1974;11:158-165.

Niemann-Pick type A disease

Autosomal recessive (MIM 257200)

In Niemann-Pick type A (NPA), the most prominent symptom is massive hepatosplenomegaly which may be congenital or may be detected in early infancy. Generally the developmental course of these infants is normal up to the age of 3-4 months and thereafter there is a progressive loss of motor and intellectual functions with severe failure to thrive. Macular cherry red spots are present in some 50% of the patients and death occur in general before the age of 3 years.

The deficiency of the lysosomal enzyme acid sphingomyelinase leads to massive storage of sphingomyelin and various phospholipids in viscera and the characteristic foam cells. The diagnosis is based on the reduction of the acid sphingomyelinase activity in leukocytes and or fibroblasts.

Epidemiology:

NPA is found with a relatively high frequency among Muslim Arabs in Israel (carrier frequency 1/50- 1/70) in the **sub districts of Petach Tiqva and Hadera as well as the region of Vadi Ara and the Lower Galilee..**

Molecular genetics:

Sphingomyelinase A SMPD1 (chromosomal locus 11p15.4-p15.1)

All the Muslim Arab patients examined were homozygous for a single mutation [677delT].

References:

Gluck I, Zeigler M, Bargal R, Schiff E, Bach G. Niemann Pick type A in Israeli Arabs: 677delT, a common novel single mutation. Hum Mut online # 161. Hum Mutat 1998; 12:136.

Niemann-Pick type C disease

Autosomal recessive (MIM 257220)

The first symptom of the disease is often a prolonged neonatal jaundice of unknown etiology with hepatosplenomegaly. In some cases it lead to hepatic failure and death before the age of 6 month, however, in most cases the jaundice resolve by itself and there is then an asymptomatic period of months or years before the appearance of the classical symptoms of the disease.

The age of onset and the progression of the disease are variable. Some of the Arab patients presented in adulthood. Most of the patients present then with neurological symptoms and splenomegaly.

Epidemiology:

The disease is relatively frequent among Arabs in Israel and the highest incidence is found in a **Bedouin tribe in the Negev**.

Molecular genetics:

NPC1 gene (chromosomal locus 18p11-q12)

The mutations responsible for the disease in most of the patients allowed were characterized (Meiner V). Among the Bedouin in the Negev a founder mutation [R404Q] was found in homozygosity in all the patients. Among the other Arab patients several different mutations were characterized: [A927V], [3347delTC], [N1156S] and [G992W]. [G992W] is the mutation that has been reported as responsible for NPD among patients from Nova Scotia)

References:

Meiner V, Shpitzen S, Mandel H, Klar A, Ben-Neriah Z, Zlotogora J, Sagi M, Lossos A, Bargal R, Sury V, Carmi R, Leitersdorf E, Zeigler M. Clinical-biochemical correlation in molecularly characterized patients with Niemann-Pick type C. Genet Med. 2001;3:343-348.

Nonbullous congenital ichthyosiform erythroderma

Autosomal recessive (MIM 242100)

Nonbullous congenital ichthyosiform erythroderma is characterized by prominent erythroderma and fine white, superficial, semiadherent scales. As many as 90% of affected individuals present at birth as collodion babies. Patients suffer from palmoplantar keratoderma, often with painful fissures, digital contractures, and loss of pulp volume. In half of the cases, a nail dystrophy including ridging, subungual hyperkeratosis, or hypoplasia has been described. Ectropion, eclabion, scalp involvement, and loss of eyebrows and lashes seem to be more frequent in NCIE than in lamellar ichthyosis. Histologic features such as hyperkeratosis, an increase in stratum corneum thickness, a normal or prominent granular layer, and increased mitoses point to a hyperproliferative epidermal defect. Prominent dermal blood vessels and an upper dermal lymphocytic infiltrate may explain the erythroderma

Epidemiology:

The disease was reported in one Muslim Arab family from the small triangle.

Molecular genetics:

ALOX12B gene (chromosomal locus 17p31)

The patient was homozygous for [p.Lys542ArgfsX]

References:

Eckl KM, de Juanes S, Kurtenbach J, Nätebus M, Lugassy J, Oji V, Traupe H, Preil ML, Martínez F, Smolle J, Harel A, Krieg P, Sprecher E, Hennies HC. Molecular Analysis of 250 Patients with Autosomal Recessive Congenital Ichthyosis: Evidence for Mutation Hotspots in ALOXE3 and Allelic Heterogeneity in ALOX12B. *J Invest Dermatol* 2009; 129:1421-1428.

Nonketotic Hyperglycinemia

Autosomal recessive (MIM 605899)

Most patients present in the neonatal period with lethargy, hypotonia and myoclonic jerks, progressing to apnea and often death. Those who regain spontaneous respiration develop intractable seizures and profound mental retardation.

NKH is an inborn error of glycine degradation in which large quantities of glycine accumulates in all body tissues including the nervous system. The diagnosis is established by calculating the CSF/plasma glycine concentration ratio (greater than 0.08) and may be confirmed by measuring the activity of the mitochondrial glycine cleavage complex in the liver. The complex includes 4 components P, H, T and L protein and since the breakdown process is sequential the absence of any of the component may cause the disorder. However, more than 80% of the patients have a deficiency in P protein and most of the other a deficiency in T protein.

Epidemiology:

The disease is relatively frequent in Israel and most of the patients originate either from a village near **Nazareth** or from **Jerusalem**. It was also found in an extended **Bedouin** family from the Negev.

Molecular genetics:

At least 4 forms of NKH may exist, each due to a defect in one of the enzyme system for cleavage of glycine

Gene amino methyl transferase (AMT) encoding for the T protein (chromosomal locus 3p21.2-p21.1)

In the village in the Galilee, all the patients are homozygote for a missense mutation [H42R].

Glycine decarboxylase (GLDC) (chromosomal locus 9p22)

In the village in the Jerusalem, all the patients are homozygote for a GLDC mutation M1V. In the Bedouin family all the patients are homozygous for a novel, translationally silent GLDC exon 22 transversion c.2607C>A

References:

- Kure S, Mandel H, Rolland MO, Sakata Y, Shinka T, Drugan A, Boneh A, Tada K, Matsubara Y, Narisawa K. A missense mutation (His42Arg) in the T-protein gene from a large Israeli-Arab kindred with nonketotic hyperglycinemia. *Hum Genet* 1998;102:430-434.
- Boneh A, Korman SH, Sato K, Kanno J, Matsubara Y, Lerer I, Ben-Neriah Z, Kure S. A single nucleotide substitution that abolishes the initiator methionine codon of the GLDC gene is prevalent among patients with glycine encephalopathy in Jerusalem. *J Hum Genet*. 2005;50:230-234.
- Flusser H, Korman SH, Sato K, Matsubara Y, Galil A, Kure S. Mild glycine encephalopathy (NKH) in a large kindred due to a silent exonic GLDC splice mutation. *Neurology*. 2005; 2664:1426-1230.

Omodysplasia

Autosomal recessive (MIM 258315)

Autosomal-recessive omodysplasia is a genetic condition characterized by proximally shortened limbs, facial dysmorphism, and severe short stature. The term omodysplasia derives from “omos,” the Greek word for humerus, and was first applied by Maroteaux to a series of patients with syndromal short stature and hypoplastic humeri. Skeletal features comprise proximal limb shortening, distal tapering of long tubular bones, proximal radioulnar diastasis, and anterolateral dislocation of the radial head. Facial features include frontal bossing, a flat nasal bridge, low set ears, a long philtrum, anteverted nostrils, and frontal capillary hemangiomas. Variable findings are cryptorchidism, hernias, congenital heart defects, and cognitive delay. Adult height ranges between 132 and 144 cm.

Epidemiology:

The disease is rare and has been described in one Muslim family in the North of Israel..

Molecular genetics:

Heparan sulfate proteoglycan glypican GPC6 *gene (chromosomal locus 13q31.1-q32.2)*. In the Muslim family a deletion in the gene was diagnosed

References:

Campos-Xavier AB, Martinet D, Bateman J, Belluoccio D, Rowley L, Tan TY, Baxova A, Gustavson K-H, Borochowitz Z U, Innes A M, Unger S, Beckmann JS Mittaz L, Ballhausen D, Superti-Furga A, Savarirayan R, Bonafe L. Mutations in the Heparan-Sulfate Proteoglycan Glypican 6 (GPC6) Impair Endochondral Ossification and Cause Recessive Omodysplasia. *Am J Hum Genet.* 2009;84:760-770.

Osteogenesis imperfecta, autosomal recessive

Autosomal recessive

Several families with recessive osteogenesis imperfecta have been reported

Molecular genetics:

FKBP10 gene (chromosomal location 17q21.2)

In a Palestinian family several affected individuals with moderately severe OI were homozygous for 1271_1272delCCinsA mutation. In a family from Jerusalem several individuals were homozygous for c.1330C>T.

CRTAP gene (chromosomal location 3p22.3)

The mutation 793+1G>T was found in homozygosity in a Bedouin family from the north of Israel (Stavit Shalev).

PP1B gene (chromosomal location 15q22.3)

The mutation c.563_566delIACAG was found in homozygosity in a Palestinian family

TMEM38B (chromosomal location 9q31.2)

A 21-kb deletion with a 12-bp insertion that resulted in deletion of exon 4 with an early stop codon and a truncated protein (c.455_542del; gly152alafs*5) was found in a Bedouin tribe from the Negev.

References:

- Barnes AM, Cabral WA, Weis M, Makareeva E, Mertz EL, Leikin S, Eyre D, Trujillo C, Marini JC. Absence of FKBP10 in recessive type XI osteogenesis imperfecta leads to diminished collagen cross-linking and reduced collagen deposition in extracellular matrix. *Hum Mutat.* 2012;33:1589-1598
- Schwarze U, Cundy T, Pyott SM, Christiansen HE, Hegde MR, Bank RA, Pals G, Ankala A, Conneely K, Seaver L, Yandow SM, Raney E, Babovic-Vuksanovic D, Stoler J, Ben-Neriah Z, Segel R, Lieberman S, Siderius L, Al-Aqeel A, Hannibal M, Hudgins L, McPherson E, Clemens M, Sussman MD, Steiner RD, Mahan J, Smith R, Anyane-Yeboa K, Wynn J, Chong K, Uster T, Aftimos S, Sutton VR, Davis EC, Kim LS, Weis MA, Eyre D, Byers PH. Mutations in FKBP10, which result in Bruck syndrome and recessive forms of osteogenesis imperfecta, inhibit the hydroxylation of telopeptide lysines in bone collagen. *Hum Mol Genet.* 2013;22:1-17
- Volodarsky M1, Markus B, Cohen I, Staretz-Chacham O, Flusser H, Landau D, Shelef I, Langer Y, Birk OS. A deletion mutation in TMEM38B associated with autosomal recessive osteogenesis imperfecta. *Hum Mutat.* 2013;34:582-586.

Osteopetrosis

Autosomal recessive (MIM 259700)

The affected patients have abnormally dense bones as well as acrocephaly, progressive deafness and blindness, hepatosplenomegaly and anemia. The various clinical features found are secondary to a functional defect in osteoclasts. The anemia is a consequence of inadequate bone marrow space that results in extra medullary hematopoiesis causing hepatosplenomegaly. The deafness and blindness represent encroachment of bone on the small foramina which house the optic and auditory nerves. The only curative therapy is bone marrow transplant with relatively good results.

Epidemiology:

The disease is estimated to be rare (1/200 000) but seems to be relatively frequent among Arabs. Several families have been diagnosed among Druze in the Galilee (Mandel H), in **the region of Jerusalem and the Territories** in particular in a village near Hebron and two extended **Bedouin pedigrees from the Negev**.

Molecular genetics:

ATP6I (TC1RG1) gene encoding for $\alpha 3$ subunit of the vacuolar proton pump (chromosomal locus 2q36-37).

Three different mutations have been found in Muslim families c.1383-1385delAAC c.C5233T c.G4640T, the last two being Bedouins. The mutation c.G4640T is frequent in one tribe from the Negev

SNX10 (chromosomal locus 7).

In three families from the region of Jerusalem a same mutation c.152G>A (Arg51Gn) was characterised. The mutation was found in one individuals among 211 controls.

References:

- Aker M, Rouvinski A, Hashavia S, Ta-Shma A, Shaag A, Zenvirt S, Israel S, Weintraub M, Taraboulos A, Bar-Shavit Z, Elpeleg O. An SNX10 mutation causes malignant osteopetrosis of infancy. *J Med Genet.* 2012;49:221-216.
- Dudin AA, Rambaud-Cousson A. Osteopetrosis and Hirschprung disease in seven children born to four consanguineous unions in two families. *Am J Med Genet* 1993; 47:1083-1085.
- Heaney C, Shalev H, Eldour K, Carmi R, Staack JB, Scheffield VC, Beier DR. Human autosomal recessive osteopetrosis maps to 11q13 a position predicted by comparative mapping to the murine osteosclerosis (oc) mutation. *Hum Mol Genet* 1998;7:1407-1410.

Oxalosis I (Primary hyperoxaluria type I)

Autosomal recessive (MIM 259900)

The condition is characterized by a continuous, high urinary oxalate excretion and progressive bilateral oxalate urolithiasis and nephrocalcinosis. Extrarenal deposits of oxalate occur in later stages. In the severe form of the disorder death from renal failure occurs in childhood or early adult life. Most of the patients have glycolicaciduria and hyperoxaluria, marked reduction in metabolism of C14-labeled glyoxylate or glycolate to carbon dioxide, increased conversion of glyoxylate to urinary glycolate. The disease is variable and there is no genotype-phenotype correlation.

Epidemiology and molecular genetics:

AGXT, gene encoding for the AGT enzyme (chromosomal locus 2q36-37)

A severe form of the disease has been diagnosed in **several villages from the Galilee**: among **Druze** and **Muslim Arabs** (Mandel H, Frishberg Y). Among those patients [A1119T] has been characterized: in a village from the lower Galilee which lead to a very severe clinical picture and [G234A]. The disease was also diagnosed in several patients from the Gaza strip [C987T and G343A] and [T853C].

A relatively mild form of the disorder was diagnosed in several patients from a Muslim Arab **village near Jerusalem** [G243A].

References:

- Choni R, Wanders RJA, Drukker A, Halle D, Frishberg Y. Primary hyperoxaluria Type I: A model for multiple mutations in a monogenic disease within a distinct ethnic group. *J Am Soc Nephrol* 1999;10:2352-2358.
- Frishberg Y, Rinat C, Shalata A, Khatib I, Feinstein S, Becker-Cohen R, Weismann I, Wanders RJ, Rumsby G, Roels F, Mandel H. Intra-familial clinical heterogeneity: absence of genotype-phenotype correlation in primary hyperoxaluria type 1 in Israel. *Am J Nephrol*. 2005;25:269-275.

Palmoplantar keratoderma punctate

Autosomal dominant (MIM 148600)

The onset is usually between ages 12 and 30 years, multiple tiny punctate keratoses over the entire palmoplantar surfaces, coalesce of the punctate keratoses into a more diffuse pattern over the pressure points of the sole, and variable nail changes. Possible association with various types of malignancy was suggested.

Epidemiology

The disorder was described in one Palestinian family from the **region of Jerusalem**.

Molecular genetics

Gene mapped on chromosome 15q22–q24.

References

Martinez-Mir A, Zlotogorski A, Londono D, Gordon D, Grunn A, Uribe E, Horev L, Ruiz IM, Davalos NO, Alayan O, Liu J, Gilliam TC, Salas-Alanis JC, Christiano AM. Identification of a locus for type I punctate palmoplantar keratoderma on chromosome 15q22–q24. *J Med Genet* 2003;40:872-878.

Parkinson disease, juvenile

Autosomal recessive (MIM 600116)

An autosomal recessive form of familial juvenile parkinsonism, defined as onset before age 40 years, has been described. JP is symptomatically different in several aspects from Parkinson disease, although classic symptoms of PD, such as bradykinesia, rigidity, and tremor, are present. At about the age of 10 years gait disturbance appear and soon the patients are unable to walk long distances. By the forties, the patients are unable to walk without assistance. There are no evidence of dementia. Slow-moving with frozen gait and tremor, more evident on motion, in the head and upper and lower limbs is evident. There is some improvement of the movement disorder after waking up in the morning.

Epidemiology

The disorder was described in one large Muslim Arab family with a begin clinical course.

Molecular genetics

Parkin gene (chromosomal locus 6q25.2-q27)

The patients were homozygous for a single base pair of adenine at nucleotide 222 of exon 2.

References

Nisipeanu P, Inzelberg R, Abo Mouch S, Carasso RL, Blumen SC, Zhang J, Matsumine H, Hattori N, Mizuno Y. Parkin gene causing benign autosomal recessive juvenile parkinsonism. *Neurology*. 2001;56:1573-1575.

Pellagra like syndrome

Autosomal recessive (MIM 260650)

In an Israeli-Arab family from the Galilee, in which the parents were first cousins 4 of 11 sibs had a pellagra-like rash with neurologic manifestations. A 14-year-old boy who was thoroughly studied had first been admitted at age 13 months with a red, scaly rash over the face, upper chest, hands, and legs. The rash disappeared with nicotinamide therapy. During childhood the pellagra-like skin rash recurred several times and was each time cured by nicotinamide. At age 14 years he showed, in addition to rash, confusion, diplopia, dysarthria, and ataxia. Again all clinical abnormalities cleared with nicotinamide. Laboratory findings excluded Hartnup disease: aminoaciduria and indicanuria were absent, as was any evidence of tryptophan malabsorption. Tryptophan loading did not induce tryptophanuria and did not increase excretion of xanthurenic or kynurenic acids.

Epidemiology:

The syndrome has been reported in a single family

Molecular genetics:

Unknown

References:

Freundlich E, Statter M, Yatziv, S. Familial pellagra-like skin rash with neurological manifestations. Arch Dis Child 1981;56:146-148.

Pendred syndrome

Autosomal recessive (MIM 274600)

Pendred first reported the association of congenital deafness and thyroid goiter in 1896. The estimated incidence is 7.5-10/10,000 and may be responsible for up to 10% of hereditary deafness. It appears that some cases are not diagnosed and such a pedigree was reported among Druze in Israel as isolated congenital deafness and was mapped to 7q31 (DNFB4) and only after the finding that the gene for Pendred syndrome was mapped in the same region reevaluation of the patients allowed to make a correct diagnosis.

Epidemiology and molecular genetics:

PDS putative sulphate transporter gene SLC26A4 gene (chromosome 7q31)

The syndrome has been reported in a large Druze kindred from a village in the Galilee. In addition, Pendred syndrome has been diagnosed in several **Bedouin** families from the **Galilee**, all with the same mutation [1421delT] even though there was no relation known between most of the families. In addition, the syndrome was also reported among **Muslim Arabs** in a village **near Jerusalem** and in a family from the region of Jerusalem. In each of the last cases a different mutation was found: [F667C] and [1565delG]

References:

- Baldwin CT, Weiss S, Farrer LA, De Stefano AL, Adair R, Franklin B, Kidd KK, Korotishevsky M, Bonne-Tamir B. Linkage of congenital recessive deafness (DNFB4) to chromosome 7q31 and evidence for genetic heterogeneity in the Middle Eastern population. *Hum Mol Genet* 1995;4:1637-1642.
- Coyle B, Coffey R, Armour JAL, Gausden E, Hochberg Z et al.. Pendred syndrome (goitre and sensorineural hearing loss) map to chromosome 7 in the region containing the non syndromic deafness gene DNFB4. *Nature Genet* 1996;12:421-423.
- Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). *Nat Genet* 1997;17:411-422.
- Sheffield VC, Kraiem Z, Beck JC, Nishimura D, Stone EM, Salameh M, Sadeh O, Glaser B. Pendred syndrome maps to chromosome 7q21-34 and is caused by an intrinsic defect in thyroid iodine organification. *Nature Genet* 1996;12:424-426.

Pelizaeus-Merzbacher-Like disease (PMLD)

Autosomal recessive (MIM 603605)

Pelizaeus-Merzbacher-Like disease (PMLD) is a hypomyelinating leukodystrophy, a disorder involving aberrant myelin formation presenting with rotatory nystagmus, progressive spastic paraplegia, severe motor impairment and neurological deterioration within the first months of life.

Molecular genetics and epidemiology

The disease is heterogenous and may be caused by homozygous mutations in GJA12 and HSPD1.

AIMP1 gene (chromosome locus4q24)

The syndrome was diagnosed in two remotely related Bedouin kindred in the Negev. In all the patients a frameshift mutation c.292_293delCA (p.Gln98ValfsX30). The mutation was not found in 190 control chromosomes.

References

Feinstein, Marcus B, Noyman I, Flusser H, Shorer Z, Shelef I, Cohen I, Khateeb S, Sivan S, Birk OS. Pelizaeus-Merzbacher-Like disease caused by a homozygous mutation in AIMP1/P43. Am J Hum Genet 2010;87:820-828.

Peroxisome Biogenesis disorders

Autosomal recessive (MIM 601539)

In the last few years progress has been made in understanding peroxisome biogenesis with at least 13 proteins identified as being necessary for this process. The names for peroxisome assembly genes and proteins are designated as 'peroxins,' with PEX representing the gene acronym.

The peroxisomal biogenesis disorders are, like the proteins of peroxisome biogenesis, a heterogeneous group with more than 10 complementation groups and with more than 1 phenotype being observed in cases falling into particular complementation groups. For example, the Zellweger syndrome, neonatal adrenoleukodystrophy or infantile Refsum disease phenotype.

Epidemiology and molecular genetics:

PEX 2 gene (chromosome 8q21.1)

The disease has been reported in one **Muslim Arab family from Vadi Ara** caused by a mutation [W223X]

References:

Gootjes J, Elpeleg O, Eyskens F, Mandel H, Mitanchez D, Shimozawa N, Suzuki Y, Waterham HR, Wanders RJ. Novel mutations in the PEX2 gene of four unrelated patients with a peroxisome biogenesis disorder. *Pediatr Res.* 2004;55:431-436.

Persistent hyperinsulinemic hypoglycemia of infancy PHHI (familial hyperinsulinism)

Autosomal recessive (MIM 600509)

The disease is characterized by profound hypoglycemia in infancy because of inadequate suppression of insulin secretion. In absence of treatment it causes seizures, coma and it may be lethal or result of irreversible neurologic sequelae.

Epidemiology:

The disease has been reported in several Bedouin and other families.

Molecular genetics

The disease is caused by mutation in either one of the 2 genes Kir 6.2 and the sulfonylurea receptor gene (SUR1) which are linked one to the other on chromosome 11p14-15.1. Each gene encodes for a subunit of the pancreatic islet alpha-cell ATP sensitive potassium (KATP) channel.

ABCC8 gene

The mutations [R836X] and [2154+3A>G] were reported among Bedouins, the mutations [R1494W] and [1113 insT] in another Arab patient.

KCNJ11 gene (chromosome 11p14-15.1)

The mutation [P254L] was reported in an Arab patient and [+88 g>t] in a Bedouin patient.

References:

- Glaser B, Philip M, Carmi R, Lieberman E, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy (nesidioblastosis): autosomal recessive inheritance in 7 pedigrees. *Am J Med Genet* 1990;37:551-515.
- Tornovsky S, Crane A, Cosgrove KE, Hussain K, Lavie J, Heyman M, Nesher Y, Kuchinski N, Ben-Shushan E, Shatz O, Nahari E, Potikha T, Zangen D, Tenenbaum-Rakover Y, de Vries L, Argente J, Gracia R, Landau H, Eliakim A, Lindley K, Dunne MJ, Aguilar-Bryan L, Glaser B. Hyperinsulinism of infancy: novel ABCC8 and KCNJ11 mutations and evidence for additional locus heterogeneity. *J Clin Endocrinol Metab*. 2004;89:6224-6234.

Peters-plus syndrome

Autosomal recessive (MIM 261540)

The features of Peters anomaly, a major error in the embryonic development of the eye, are corneal clouding and variable iridolenticulocorneal adhesions. The association of Peters anomaly and short-limb dwarfism was reported in 2 cousins and an unrelated patient, all offspring of consanguineous parents. They presented also with communicating hydrocephalus (or brain atrophy) and polyhydramnios.

Epidemiology:

The syndrome has been reported only in a single large kindred.

Molecular genetics:

Unknown

References:

Frydman M, Weinstock AL, Cohen HA, Savir H, Varsano I. Autosomal recessive Peters anomaly, typical facial appearance, failure to thrive, hydrocephalus, and other anomalies: further delineation of the Krause-Kivlin syndrome. *Am J Med Genet* 1991;40: 34-40.

Phenylketonuria

Autosomal recessive (MIM 261600)

In Israel several Arab families have been diagnosed with PKU and the incidence of is 1:6,000 live births (1995-1998).

Molecular genetics:

The most frequent mutation [IVS10nt546] among Arabs was also found in Europe on a same haplotype indicating a possible gene flow from there. The 2 mutations [R408W] and [R261Q] are also present in other populations while other mutations are unique to the Palestinian Arabs such as [IVSnt2], [Edel(197-205)] and [R270S].

References:

Kleiman S, Avigad S, Vanagaite L, Shmuelewitz A, David M et al.. Origin of hyperphenylalaninemia in Israel. Eur J Hum Genet 1994;2:24-34.

Phosphorylase kinase deficiency of liver and muscle

Autosomal recessive (MIM 261750)

In an Israeli Arab family, a 4-year-old brother and 2 sisters had marked hepatomegaly and marked accumulation of glycogen in both liver and muscle, without clinical symptoms. Liver phosphorylase kinase (PK) activity was 20% of normal, resulting in undetectable activity of phosphorylase a. Muscle PK was about 25% of normal, resulting in a marked decrease of phosphorylase a activity.

Epidemiology:

The syndrome has been reported only in a single family

Molecular genetics:

Unknown

References:

Bashan N, Iancu TC, Lerner A, Fraser D, Potashnik R, Moses SW. Glycogenosis due to liver and muscle phosphorylase kinase deficiency. *Pediat Res* 1981;15:299-303.

Pituitary hormone deficiency (combined)

Autosomal recessive (MIM 173110)

Mutations of the POU1F1 gene is responsible for pleiotropic deficiencies of growth hormone, prolactin, and thyroid-stimulating hormone, while the production of adrenocorticotrophic hormone, luteinizing hormone and follicle-stimulating hormone are preserved.

Epidemiology:

The disorder has been diagnosed in several **Arab families**.

Molecular genetics:

POU1F1 gene (chromosome 3p11)

One mutation was found in each of the Muslim Arab families F262L and W193X respectively. In one Arab family the patient was homozygous for K230E. A patient from the Galilee was homozygous for c.502insT(p.Thr168IlefsX7).

References:

- Gat-Yablonski G, Klar A, Hirsch D, Eliakim A, Lazar L, Hurvitz H, Phillip M. Three novel mutations in POU1F1 in Israeli patients with combined pituitary hormone deficiency. J Pediatr Endocrinol Metab. 2005;18:385-393.
- Gat-Yablonski G, Lazar L, Pertzalan A, Phillip M. A novel mutation in PIT-1: phenotypic variability in familial combined pituitary hormone deficiencies. J Pediatr Endocrinol Metab. 2002;15:325-330.
- Tenenbaum-Rakover Y, Sobrier ML, Amselem S. A novel POU1F1 mutation (p.Thr168IlefsX7) associated with an early and severe form of combined pituitary hormone deficiency: functional analysis and follow-up from infancy to adulthood. Clin Endocrinol (Oxf). 2011;1365-22652011

PNPO (Pyridoxamine 5'-phosphate oxidase) deficiency

Autosomal recessive (MIM 610090)

Patients are born prematurely and have low Apgar scores and/or required intubation. Early acidosis is common. Thus, PNPO deficiency must enter the differential diagnosis of hypoxic-ischemic encephalopathy in a prematurely born infant. Seizures usually begin on the first day of life, with EEG showing a burst suppression pattern. Biochemical abnormalities in CSF and urine were as for aromatic L-amino acid decarboxylase deficiency. In some cases seizures may respond to pyridoxal phosphate (PLP).

Epidemiology:

The disorder has been diagnosed in a **large inbred Muslim Arab family**.

Molecular genetics:

Pyridoxamine 5-prime-phosphate oxidase PNPO gene (chromosome 17q21.32)

The patient was homozygous for a G>A transition at nucleotide 284 in exon 3 (c.284 G>A) resulting in a R95H missense mutation

References:

Khayat M, Korman SH, Frankel P, Weintraub Z, Herschkowitz S, Sheffer VF, Elisha MB, Wevers RA, Falik-Zaccai TC. PNPO deficiency: An under diagnosed inborn error of pyridoxine metabolism. *Mol Genet Metab.* 2008; 94:431-444.

Polymicrogyria, bilateral frontal

Autosomal recessive (MIM 606864)

The patients share a congenital syndrome of developmental delay, moderate to severe mental retardation, seizures, esotropia, pyramidal signs, cerebellar impairment and bilateral polymicrogyria which was more prominent in the frontal and parietal lobes.

Polymicrogyria is a cerebral cortical malformation that is grossly characterized by excessive cortical folding and microscopically characterized by abnormal cortical layering. The identification of the cortical abnormality as polymicrogyria is based on characteristic scalloped appearance of the border between gray and white matter. It is demonstrated by thinner cuts in MRI sections.

Epidemiology:

The disorder has been diagnosed in two **Muslim Arab** pedigrees from two different villages in the **central region of Israel**.

Molecular genetics:

GPR56 (chromosome 16q12.2-21)

One mutation was found in each of the villages [IVS9+3G-C] and [C346S] respectively.

References:

- Piao X, Basel-Vanagaite L, Straussberg R, Grant PE, Pugh EW, Doheny K, Doan B, Hong SE, Shugart YY, Walsh A. An autosomal recessive form of bilateral frontoparietal polymicrogyria maps to chromosome 16q12.2-21. *Am J Hum Genet* 2002; 70:1028-1033.
- Piao X, Hill RS, Bodell A, Chang BS, Basel-Vanagaite L, Straussberg R, Dobyns WB, Qasrawi B, Winter RM, Innes AM, Voit T, Ross ME, Michaud JL, Descarie JC, Barkovich AJ, Walsh CA G protein-coupled receptor-dependent development of human frontal cortex. *Science*. 2004; 303:2033-2036.

Polycystic kidneys, autosomal recessive

Autosomal recessive (MIM 263200)

Childhood polycystic kidneys disease was classified into 4 classes according to the age of onset, clinical course proportion of renal tubules involved and degree of hepatic fibrosis. However, it was demonstrated that the variability is present within families and therefore is not genetic.

Epidemiology:

Among Arabs in Israel the disease has been diagnosed in several Arab families., in particular in 18 **Bedouin patients from the Negev**.

Molecular genetics

PKHD1 (chromosome 6p21)

The disease is caused by mutations PKHD1 that is very large. The mutations in the Bedouin patients were not characterized but linkage to the gene was demonstrated.

References:

Landau D, Shalev H, Shulman H, Barki Y, Maor E, Zmora E. Oligohydramnion, renal failure and no pulmonary hypoplasia in glomerulocystic kidney disease. *Pediatr Nephrol* 2000;14:319-321.

Feiner G, Birk O, Landau. Genetic and phenotypic aspects of autosomal recessive polycystic kidney disease patients in the Negev. *Harefua* 2004; 143:466-470.

Polymalformative syndrome due to FTO mutation

Autosomal recessive (MIM 610966)

In a large inbred family including 9 affected children presenting a syndrome characterized by severe intra-uterine growth and psychomotor retardation, microcephaly, delayed myelinization, cleft palate, cardiac and genital anomalies, hypertonicity. Early lethality 1-30 months was also reported.

Epidemiology:

The Muslim Arab family is living in the center of Israel.

Molecular genetics

FTO gene (chromosome 16q12)

All the patients were homozygous missense variation within the FTO gene [c.947G>A], p.R316Q

References:

Boissel S, Reish O, Proulx Ke, Kawagoe-Takaki H, Sedgwick B., Yeo GSH, Meyre D, Golzio C, Molinari F, Kadhon N, Etchevers HC, Saudek V, Farooqi IS, Froguel P, Lindahl T, O'Rahilly S, Munnich A, Colleaux L. Loss-of-Function Mutation in the Dioxygenase-Encoding FTO Gene Causes Severe Growth Retardation and Multiple Malformations. *Am J Hum Genet.* 2009; 85:106-1111.

Pontocerebellar hypoplasia

Autosomal recessive (MIM 607596)

Pontocerebellar hypoplasia (PCH) is classified into several types based on the clinical picture and the spectrum of pathologic changes. In PCH type 1, with anterior horn degeneration, there is central and peripheral motor dysfunction from birth leading to early death, mostly before 1 year of age. PCH and gliosis are seen in association with anterior horn cell degeneration resembling infantile spinal muscular atrophy. In PCH type 2 there is progressive microcephaly from birth combined with extrapyramidal dyskinesia. Motor or mental development is nil, severe chorea occurs, and epilepsy is frequent, while signs of spinal anterior horn involvement are lacking.

Epidemiology:

PCH type 2 has been diagnosed in a Muslim Arab family.

Molecular genetics:

TSEN54 (chromosome 17q25.1)

The mutation [A307S] was found in homozygosity, the same mutation has been reported in several families of European descent and was characterized there as a founder mutation.

References:

Budde BS, Namavar Y, Barth PG, Poll-The BT, Nürnberg G, Becker C, van Ruissen F, Weterman MA, Fluiter K, T Te Beek E, Aronica E, van der Knaap MS, Höhne W, Tolia MR, Crow YJ, Steinlin M, Voit T, Roelens F, Brussel W, Brockmann K, Kyllerman M, Boltshauser E, Hammersen G, Willemsen M, Basel-Vanagaite L, Krägeloh-Mann I, de Vries LS, Sztriha L, Muntoni F, Ferrie CD, Battini R, Hennekam RC, Grillo E, Beemer FA, Stoets LM, Wollnik B, Nürnberg P, Baas F. tRNA splicing endonuclease mutations cause pontocerebellar hypoplasia. *Nat Genet.* 2008; 40:1113-1118

POR deficiency

Autosomal recessive (MIM 201750)

P450 oxyreductase deficiency is a rare variant of congenital adrenal hyperplasia. The most striking phenotypic feature is that affected girls are born with ambiguous genitalia, indicating intrauterine androgen excess. After birth however, virilization does not progress, and amounts of circulating androgens are low or normal. Conversely, affected boys are sometimes born undermasculinized. Boys and girls can also present with bone malformations of the type seen in Antley-Bixler syndrome.

Epidemiology:

Several patients were reported from a small Bedouin clan in the Negev

Molecular genetics

POR deficiency (chromosome 7q11.2)

All the Bedouin patients were homozygous for G539R

References:

Hershkovitz E, Parvari R, Wudy SA, Hartmann MF, Gomes LG, Loewental N, Miller WL. Homozygous mutation G539R in the gene for P450 oxidoreductase in a family previously diagnosed as having 17,20 lyase deficiency. *J Clin Endocrinol Metab.* 2008; 93:3584

Primary ciliary dyskinesia (PCD)

Autosomal recessive (MIM 244400)

PCD is a disorder characterised by respiratory tract infections, sinusitis, bronchiectasis and subfertility. It affects 1:20,000 live births. The clinical phenotype results from dysmotility of the cilia, which is associated with a variety of structural abnormalities. The core or axoneme of cilia comprises a bundle of microtubules and associated proteins including dyneins, nexin links and radial spokes. About 50% of patients exhibit laterality defects, commonly situs inversus, known as Kartagener syndrome.

Epidemiology:

Among **Druze** in Israel the disease has been reported in 4 families from two villages in the **Golan Heights**. The disorder was also reported in a large Bedouin family from the center of Israel and two families from the Negev

Molecular genetics:

CILD8 (chromosome locus 15q24-q25)

In the Druze kindred genome wide scan identified a region consistent with linkage in three of the four families on chromosome 15q13.1-15.1.

RSPH 9 (chromosome locus 6p21.1)

In the Bedouin family from the center of Israel the patients were homozygous for c.801_803delGAA

CCDC39(chromosome locus 3)

In a Druze family from the Golan Heights the mutation p.Glu471X (c.1410G>T) was found in homozygosity

DNAL1 (chromosome locus 14q24.2-q31.31)

In the two Bedouin families from the Negev the patients were homozygous for c.449A>G p.Asn150Ser

References:

- Castleman VH, Romio L, Chodhari R, Hirst RA, de Castro SC, Parker KA et al. Mutations in radial spoke head protein genes RSPH9 and RSPH4A cause primary ciliary dyskinesia with central-microtubular-pair abnormalities. *Am J Hum Genet.* 2009; 84:197-209.
- Jeganathan D, Chodhari R, Meeks M, Faeroe O, Smyth D, Nielsen K, Amirav I, Luder AS, Bisgaard H, Gardiner RM, Chung EM, Mitchison HM. Loci for primary ciliary dyskinesia map to chromosome 16p12.1-12.2 and 15q13.1-15.1 in Faroe Islands and Israeli Druze genetic isolates. *J Med Genet* 2004;41:233-240.
- Merveille AC, Davis EE, Becker-Heck A, Legendre M, Amirav I, Bataille G et al. CCDC39 is required for assembly of inner dynein arms and the dynein regulatory complex and for normal ciliary motility in humans and dogs. *Nat Genet.* 2011;43:72-78.
- Mazor M, Alkrinawi S, Chalifa-Caspi V, Manor E, Sheffield VC, Aviram M, Parvari R. Primary Ciliary Dyskinesia Caused by Homozygous Mutation in DNAL1, Encoding Dynein Light Chain 1 *Am J Hum Genet* 2011; 88:599-607

Progressive myoclonic epilepsy-ataxia

Autosomal recessive (MIM 608500)

The first signs of the disease begin with ataxia at the age of 4 years. Myoclonus usually appears later and worsens. The cognitive decline is mild or absent

Epidemiology

Several patients were diagnosed in Palestinian Arab families from Israel and Jordan

Molecular genetics:

Prickle1 gene (Chromosome 12q12)

All the patients were homozygous for [R104Q]

References:

Bassuk AG, Wallace RH, Buhr A, Buller AR, Afawi Z, Shimojo M, Miyata S, Chen S, Gonzalez-Alegre P, Griesbach HL, Wu S, Nashelsky M, Vladar EK, Antic D, Ferguson PJ, Cirak S, Voit T, Scott MP, Axelrod JD, Gurnett C, Daoud AS, Kivity S, Neufeld MY, Mazarib A, Straussberg R, Walid S, Korczyn AD, Slusarski DC, Berkovic SF, El-Shanti HI. A Homozygous Mutation in Human PRICKLE1 Causes an Autosomal-Recessive Progressive Myoclonus Epilepsy-Ataxia Syndrome. *Am J Hum Genet.* 2008; 83:572-581. Berkovic SF, Mazarib A, Walid S, Neufeld MY, Manelis J, Nevo Y, Korczyn AD, Yin J, Xiong L, Pandolfo M, Mulley JC, Wallace RH. A new clinical and molecular form of Unverricht-Lundborg disease localized by homozygosity mapping. *Brain.* 2005;128:652-658.

Progressive Myoclonic epilepsy Unverrich-Lundborg

Autosomal recessive (MIM 254800)

The first signs of the disease begin at the age of 6-13 years with convulsions. Myoclonus usually appears the year later predominantly in the extremities. The disease is characterized by a severe stimulus sensitive myoclonic and generalized seizures as well as neurologic deterioration including dementia and ataxia.

Epidemiology

Several patients were diagnosed in a **large Arab pedigree from a large village in the Galilee**.

Molecular genetics:

Cystatin B gene CSTB (chromosomal locus 21q22.3)

In the pedigree all the Arab patients from the Galilee, homozygosity for an expansion mutation was characterized.

References:

Berkovic SF, Mazarib A, Walid S, Neufeld MY, Manelis J, Nevo Y, Korczyn AD, Yin J, Xiong L, Pandolfo M, Mulley JC, Wallace RH. A new clinical and molecular form of Unverricht-Lundborg disease localized by homozygosity mapping. *Brain*. 2005;128:652-8.

Mazarib A, Xiong, Neufeld MY, Birnbaum M, Korczyn AD, Pandolfo M, Berkovic SF, Unverricht-Lundborg disease in a five generation arab family, *Neurology* 2001;57:1050-1054.

Prolidase deficiency

Autosomal recessive (MIM 170100)

Clinical features included chronic dermatitis, frequent infections, splenomegaly, and massive iminodipeptiduria. Dermatologic features, particularly severe leg ulcers, and mental retardation of variable severity are the main manifestations.

Prolidase, the enzyme known to cleave the bond between the other amino acid and proline (which is carboxyl-terminal), is absent or markedly decreased in the patient's red and white cells. One or more of the symptoms of prolidase deficiency may reflect a tissue deficiency of L-proline, which is not reclaimed in the absence of prolidase. Excretion of this amino acid, in bound form, can be as high as 20 to 30 mmol/day. Against the proposition that the failure of recovery of proline from iminodipeptides has a major role in the pathogenesis of prolidase deficiency is the fact that oral administration of L-proline does not relieve the dermatologic lesions. Attempts at enzyme replacement with normal matched erythrocytes have had no effect on iminodipeptiduria and this appears to be due to the fact that prolidase occurs in erythrocytes in an inactive form.

Epidemiology

Several Arab patients have been diagnosed and the disease is relatively frequent in several villages.

Molecular genetics:

Peptidase D gene PEPD (chromosomal locus 19cen-q13.11)

In once Druze patient with hyper IgE an homozygous C605T mutation was found

References:

- Mandel H, Abeling N, Gutman A, Berant M, Scholten EG, Luder A, van Gennip AH. Prolidase deficiency among an Israeli population: prenatal diagnosis in a genetic disorder with uncertain diagnosis. *Prenatal Diag* 2000;20:927-929.
- Hershkovitz T, Hassoun G, Indelman M, Shlush LI, Bergman R, Pollack S, Sprecher E.A homozygous missense mutation in PEPD encoding peptidase D causes prolidase deficiency associated with hyper-IgE syndrome. *Clin Exp Dermatol*. 2006;31:435-440.

Pseudorheumatoid arthropathy of childhood

Autosomal recessive (MIM 208230)

The disorder has a striking clinical, though not radiologic, resemblance to rheumatoid arthritis but has the additional feature of platyspondyly. All the patients are considered normal for the first few years of life and joint symptoms begin between ages 3 and 8 years. Usually several joints are affected with pain and soft tissue swelling. The proximal interphalangeal joints of the hand are most commonly affected and the hips and elbows next most often involved.

Epidemiology

Several patients were diagnosed in a **large Arab pedigree a single village in the Galilee** (Shalev S).

Molecular genetics:

WISP3 gene B (chromosomal locus 6q22-q23)

In one village from the Galilee, homozygosity for a same mutation [552delGT] was characterized. A bedouin patient from Jerusalem was homozygous for a mutation.

References:

Delague V, Chouery E, Corbani S, Ghanem I, Aamar S, Fischer J, Levy-Lahad E, Urtizberea JA, Mégarbané A. Molecular study of WISP3 in nine families originating from the Middle-East and presenting with progressive pseudorheumatoid dysplasia: identification of two novel mutations, and description of a founder effect. *Am J Med Genet A*. 2005;138A:118-226.

Pseudohermaphroditism, male with gynecomastia

Autosomal recessive (MIM 264300, 60557317)

The affected males are born with female looking external genitalia and reared as such until puberty if not diagnosed before. At puberty male virilization occur and adult develop male body habitus, with abundant body hair and beard and the phallus and testes enlarge to adult proportions. The diagnosis may be done in infancy because of the presence of inguinal testis which are often diagnosed as inguinal hernia.

The basic defect is a deficiency in 17 β hydroxysteroid dehydrogenase 3 which is responsible for the synthesis of testosterone by human testes. The enzyme prefers androstendione as substrate and is almost expressed exclusively in the testis.

Epidemiology and molecular genetics:

17 β hydroxysteroid dehydrogenase type 3 gene (chromosomal locus 9q22)

Pseudohypoaldosteronism type I

Autosomal recessive (MIM 264350)

In the autosomal recessive form of PHA I, symptoms are typically severe and persist into adulthood. The disease is characterized by salt wasting in infancy that is responsive to supplementary sodium but not to mineralocorticoids. Marked aldosterone excess is present in all reported cases and the renin level is increased in most. Sweat and salivary glands and colonic mucosa are unresponsive to mineralocorticoids as is the distal renal tubule.

Epidemiology and Molecular genetics:

SCNN1B gene (chromosomal locus 16p13-p12)

In a Palestinian Arab kindred the mutation c.236G>A (Gly37Ser) was found in all the patients. In another Israeli muslim patient the mutation 1669+1G>A was found in homozygosity.

References

Chang SS, Grunder S, Hanukoglu A, Rösler A, Mathew PM, Hanukoglu I, Schild L, Lu Y, Shimkets RA, Nelson-Williams C, Rossier BC, Lifton RP. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. *Nat Genet.* 1996;12:248-253

Edelheit O, Hanukoglu I, Shriki Y, Tfilin M, Dascal N, Gillis D, Hanukoglu A. Truncated beta epithelial sodium channel (ENaC) subunits responsible for multi-system pseudohypoaldosteronism support partial activity of ENaC. *J Steroid Biochem Mol Biol.* 2010;119:84-88..

Pycnodysostosis

Autosomal recessive (MIM 265800)

The syndrome is characterized by short stature, generalized increased bone density (osteosclerosis) separated cranial sutures with open fontanelles, loss of mandibular angle, dysplastic lateral clavicles, partial dissolution of the terminal phalanges of the hand and bone fragility. The patients are generally short limb dwarfs measuring no more than 152 cms. They have large head with frontal and occipital prominence. There is a relative underdevelopment of the facial bones in particular the mandible and often a large nose. The patients present with normal intelligence and have a normal life span.

The metabolic basis of the disease was discovered after the mapping and cloning of the responsible gene cathepsin K. The gene encodes for a lysosomal enzyme which is a major protease in bone resorption. The disorder is therefore unique among lysosomal disorders since it is not secondary to storage but to a defective tissue specific expression.

Epidemiology:

The disease has been reported in 14 patients from a large kindred in **a single village in the Galilee**.

Molecular genetics:

cathepsin K (chromosomal locus 1q21)

All the patients were found to be homozygote for a A to G transition which lead to the substitution of the termination codon by a tryptophan residue and the elongation of the COOH terminus by 19 additional amino acids [X330W].

References:

- Edelson JG, Obad S, Geiger R, On A, Artul HJ. Pycnodysostosis. Orthopedic aspects with a description of 14 new cases. Clin Ortho 1992;280: 263-276.
- Gelb BD, Shi GP, Chapman HA, Desnick RJ. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. Science 1996;273:1236-1238.

Refsum disease, infantile form

Autosomal recessive (MIM 266510)

Patients with the infantile form of phytanic acid storage disease show both clinical and biochemical differences from patients with the classic form of Refsum disease. Features include early onset, mental retardation, minor facial dysmorphism, retinitis pigmentosa, sensorineural hearing deficit, hepatomegaly, osteoporosis, failure to thrive, and hypocholesterolemia. The biochemical abnormalities are not restricted to phytanic acid but also include accumulation of very long chain fatty acids (VLCFA), di- and trihydroxycholestanoic acid and pipecolic acid. Deficiency of peroxisomes in hepatocytes and cultured skin fibroblasts is demonstrable. Clinically, infantile Refsum disease, ZWS, and adrenoleukodystrophy have several overlapping features. Biochemically, IRD patients show accumulation of phytanic acid as in the classic form of Refsum disease but in addition they show defective bile acid metabolism as in Zellweger syndrome

Epidemiology:

No data

Molecular genetics:

No data

References:

Goez H, Meiron D, Horowitz J, Schutgens R H, Wanders R J A, Berant M, Mandel H. Infantile Refsum disease: neonatal cholestatic jaundice presentation of a peroxisomal disorder. *J Pediatr Gastroenterol Nutr* 1999;520:98-101.

Renal proximal tubulopathy with hypercalciuria

Autosomal recessive (MIM)

Three children (2 girls, 1 boy) presented with renal glycosuria and hypercalciuria. Evaluation of the 3 affected children showed glycosuria, generalized aminoaciduria, hypouricemia, uricosuria, low molecular weight (LMW) proteinuria, and hypercalciuria in all 3 children and phosphaturia in 2 children. They had no metabolic acidosis or renal insufficiency. One affected girl had nephrocalcinosis. Two children had a history of growth retardation and radiological findings of metabolic bone disease.

Epidemiology:

The syndrome has been reported in a highly consanguineous Druze family

Molecular genetics:

Unknown

References:

Magen D, Adler L, Mandel H, Efrati E, Zelikovic I. Autosomal recessive renal proximal tubulopathy and hypercalciuria: a new syndrome. *Am J Kidney Dis.* 2004;43:600-606.

Renal glucosuria

Autosomal recessive (MIM 233100)

Familial renal glucosuria (FRG) is an isolated disorder of proximal tubular glucose transport, characterized by abnormal urinary glucose excretion in the presence of normal blood glucose levels. Generalized aminoaciduria has not generally been considered a feature of this disorder.

In three unrelated families residing in two different villages six affected children were asymptomatic, but displayed massive glucosuria accompanied by generalized aminoaciduria.

Epidemiology:

The syndrome has been reported in Muslim Arab families two close villages in the Galilee.

Molecular genetics:

Sodium glucose transporter SLC5A2 (chromosomal locus 16p11.2)

All the affected patients were homozygous for the mutation K321R.

References:

Magen D, Sprecher E, Zelikovic I, Skorecki K. A novel missense mutation in SLC5A2 encoding SGLT2 underlies autosomal-recessive renal glucosuria and aminoaciduria. *Kidney Int* 2005;67:34-41.

Renal hypouricemia

Autosomal recessive (MIM 612076)

Most of the patients are asymptomatic; some have nephrolithiasis and have a predisposition to exercise induced acute renal failure

Epidemiology and Molecular genetics:

SLC2A9 (chromosomal locus 16p11.2)

The syndrome has been reported in a Bedouin kindred living in the center of israel originating from the Negev. All the patients were homozygous for L75R.

References:

Dinour D, Gray NK, Campbell S, Shu X, Sawyer L, Richardson W, Rechavi G, Amariglio N, Ganon L, Sela BA, Bahat H, Goldman M, Weissgarten J, Millar MR, Wright AF, Holtzman EJ Homozygous SLC2A9 mutations cause severe renal hypouricemia. J Am SocNephrol. 2010;21:64-72.

Renal tubular dysgenesis

Autosomal recessive (MIM 267430)

Affected children present with oligohydramnios sequence and pulmonary hypoplasia and show a seemingly unique histologic change in the kidneys. Normal proximal convoluted tubules are absent and all tubules appear abnormally developed, primitive and reminiscent of collecting tubules. hypoplasia of all segments of the nephron, from the glomerulus to the collecting tubule.

Early prenatal diagnosis may be difficult because amniotic fluid volumes have been shown to be normal in affected pregnancies before the 22nd week of gestation. Late second trimester sonographic demonstration of oligohydramnios, with structurally normal kidneys, should suggest the diagnosis and the need for detailed postmortem pathologic examination for this disorder, which may not be rare.

Epidemiology:

The syndrome has been reported in several families.

Molecular genetics:

Unknown

References:

Ariel I, Wells TR, Landing BH, Sagi M, Bar-Oz B, Ron N, Rosenmann E. Familial renal tubular dysgenesis: a disorder not isolated to proximal convoluted tubules. *Pediatr Pathol Lab Med* 1995;15:915-922.

Renal tubular acidosis with progressive sensorineural deafness

Autosomal recessive (OMIM 267300)

The disease present either acutely with dehydration and vomiting, or with failure to thrive and/or growth impairment. In each case, the diagnosis is based on inappropriately alkaline urine (pH greater than 5.5) and the presence of systemic metabolic acidosis with normal anion gap, evidence of renal potassium wasting, and no evidence of secondary causes of dRTA. All patients, including infants, had nephrocalcinosis, accompanied by elevated urinary calcium and rickets is also found. The renal function is normal.

Epidemiology:

The disease was reported in one Bedouin family from the Negev and one Muslim family from the Galilee.

Molecular genetics:

ATP6V1B1 gene (chromosomal locus 2 cent-q13)

The Bedouin patients were homozygous for mutation 340C>T, the patient from the Galilee was homozygous for a splice junction mutation before exon 4

References

Joshua B, Kaplan DM, Raveh E, Lotan D, Anikster Y. Audiometric and imaging characteristics of distal renal tubular acidosis and deafness. *J Laryngol Otol. J Laryngol* 2008 ;122:193-198.

Resistance to thyrotropin

Autosomal recessive (MIM 122560, 603372)

Resistance to thyrotropin is a condition of impaired responsiveness of the thyroid gland to TSH characterized by elevated TSH, low to normal thyroid hormone levels and hypoplastic or normal sized thyroid gland.

Epidemiology:

The disease has been reported in several individuals in an Arab town in the "triangle". The carrier frequency of the mutations in this town were 1.2% for L653V and 0.9% for P68S.

Molecular genetics:

Thyrotropin receptor TSHR (chromosomal locus 14q31).

Two TSHR mutations P68S and L653V were identified in a large kindred all presenting with compensated RTSH with high TSH and normal T3 and T4

References:

Tenenbaum-Rakover Y, Grasberger H, Mamasiri S, Ringkananont U, Montanelli L, Barkoff MS, Dahood AM, Refetoff S. Loss-of-Function Mutations in the Thyrotropin Receptor Gene as a Major Determinant of Hyperthyrotropinemia in a Consanguineous Community. *J Clin Endocrinol Metab.* 2009; 94:1706-1712.

Reticulosis, familial hystiocytic - Familial hemophagocytic lymphohistiocytosis.

Autosomal recessive (MIM 267700)

Most patient have fever, wasting, and hepatosplenomegaly. Lymph node enlargement and neurologic abnormalities were common. The most consistent laboratory findings is pancytopenia, atypical lympho-monocytoid cells in the peripheral blood, abnormal liver function tests, and increased CSF protein. Death occurred in rule rapidly after diagnosis..

Incidence:

This very rare disorder has been reported in one patient from a village from the center region.

Molecular studies:

The disease is heterogeneous

FHL3, Munc13-4 gene (chromosomal locus 17q25)

The patient was homozygous for the mutation [1755 insT].

References:

Feldmann J, Callebaut I, Raposo G, Certain S, Bacq D, Dumont C, Lambert N, Ouachee-Chardin M, Chedeville G, Tamary H, Minard-Colin V, Vilmer E, Blanche S, Le Deist F, Fischer A, de Saint Basile G. Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). *Cell* 2003; 115:461-473.

Retinitis pigmentosa

Autosomal recessive (MIM 268000)

Retinitis pigmentosa is characterized by constriction of the visual fields, night blindness, and fundus changes, including 'bone corpuscle' lumps of pigment. RP unassociated with other abnormalities is inherited most frequently as an autosomal recessive inheritance.

Molecular genetics and epidemiology:

TULP1 (chromosomal locus 6p21.31) (MIM 600132)

In a large consanguineous Muslim Arab family several individuals with early onset RP were homozygous for c.1495+2_1495+insT (not detected in 114 random Muslim Arab Arabs)

PRCD (chromosomal locus 17q22)(MIM 610599)

RP is particularly frequent in an Muslim Arab village in the Galilee in which all the affected are homozygous for R22X with a 10% carrier frequency in the village.

PDE6G (chromosomal locus 17q25.3)(MIM 180073)

RP is particularly frequent in an Muslim Arab village in the Galilee in which all the affected are homozygous for c.187+1G>T with a 8.3% carrier frequency in the village.

C2ORF71(chromosomal locus 2p23.1-p24.1)

In each of two Muslim families a homozygous mutation was reported c.556C>T and c.2756_2768del

C8ORF37(chromosomal locus 8q22.1)

In a Druze family RP with onset at 18 with early macular involvement was diagnosed in a patient with c.545A>G

References:

- Abbasi AH, Garzozzi HJ, Ben-Yosef T. A novel splice-site mutation of TULP1 underlies severe early-onset retinitis pigmentosa in a consanguineous Israeli Muslim Arab family. *Mol Vis.* 2008;14:675-682.
- Collin RW, Safieh C, Littink KW, Shalev SA, Garzozzi HJ, Rizer L, Abbasi AH, Cremers FP, den Hollander AI, Klevering BJ, Ben-Yosef T. Mutations in C2ORF71 cause autosomal-recessive retinitis pigmentosa. *Am J Hum Genet.* 2010;86:783-7788.
- Dvir L, Srour G, Abu-Ras R, Miller B, Shalev SA, Ben Yosef T. Autosomal recessive early onset retinitis pigmentosa caused by a mutation in PDE6G, the gene encoding the gamma subunit of rod cGMP phosphodiesterase. *Am J Hum Gene* 2010; 87: 1-7
- Nevet MJ, Shalev SA, Zlotogora J, Mazzawi N, Ben-Yosef T. Identification of a prevalent founder mutation in an Israeli Muslim Arab village confirms the role of PRCD in the aetiology of retinitis pigmentosa in humans. *J Med Genet.* 2010;47:533-537
- Estrada-Cuzcano A, Neveling K, Kohl S, Banin E, Rotenstreich Y, Sharon D, Falik-Zaccai TC, et al. Mutations in C8orf37, Encoding a Ciliary Protein, are Associated with Autosomal-Recessive Retinal Dystrophies with Early Macular Involvement. *Am J Hum Genet.* 2012;90:102-109.

Rickets, 1,25 dehydroxyvitamin D₃ resistant

Autosomal recessive (MIM 277440)

The disease has typically its onset in infancy with the appearance of severe rickets, hypocalcemia, secondary hyperparathyroidism and elevated 1,25(OH)₂D₃ circulating levels. A frequent associated finding is total scalp and body alopecia.

Epidemiology:

The disease has been reported in seven related families from a village near Haifa.

Molecular genetics:

Vitamin D receptor gene, VDR (chromosomal locus 12q12-q14)

All the patients are homozygous for a tyr to ter in codon 292 of exon 7.

References:

Malloy PJ, Hochberg Z, Tiosano D, Pike JW, Hughes MR, Feldman D. The molecular basis of hereditary 1,25 dehydroxyvitamin D₃ resistant rickets in seven related families. *J clin Invest* 1990;86:2071-2079.

Rickets, hereditary hypophosphatemic autosomal recessive

Autosomal recessive (MIM 241530)

The main manifestations are short stature and bowing legs with laboratory hypophosphatemia

Epidemiology:

The syndrome has been reported a **Bedouin tribe from the Negev**.

Molecular genetics:

ENPP1 gene (chromosomal locus 6q22-q23)

In the Bedouin tribe all the the patients were homozygous for a same mutation Y901S

In another Muslim Arab family from Israel the patient was homozygous for c2248_2249insA

References:

Levy-Litan V, HersHKovitz E, Avizov L, Leventhal N, Bercovich D, Chalifa-Caspi V, Manor E, Buriakovsky S, Hadad Y, Goding J, Parvari R. Autosomal-Recessive Hypophosphatemic Rickets Is Associated with an Inactivation Mutation in the ENPP1 Gene. *Am J Hum Genet.* 2010;86:273-278.

Lorenz-Depiereux B, Schnabel D, Tiosano D, Häusler G, Strom TM. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. *Am J Hum Genet.* 2010;86:267-272.

Rickets, hereditary hypophosphatemic with hypercalciuria

Autosomal recessive (MIM 241530)

The disease was first reported in several individuals from a **Bedouin** tribe. The clinical and histopathological features are typical of rickets or osteomalacia but the biochemical profile is distinct. According to the metabolic studies it seems that these individuals have a mild hereditary renal phosphate leak. The magnitude of the hypophosphatemia which regulates 1,25(OH)₂D levels appears to determine which subjects will have hypercalciuria alone and which will also have a bone disease. The heterozygotes often show hypercalciuria often with mild hypophosphatemia.

Epidemiology:

The syndrome has been reported in a large **Bedouin tribe** and several Arab families in Israel.

Molecular genetics:

SLC34A3 (chromosomal locus 9q34)

In the large Bedouin tribe the patients are homozygous for c.228delC. The other mutations found were c.905delC, c.1058 G>T (R353L), c.1238C>A (A413E) and c.846G>A.

References:

Bergwitz C, Roslin NM, Tieder M, Loredó-Ostí JC et al. SLC34A3 mutations in patients with hereditary hypophosphatemic with hypercalciuria predict a key role for the sodium phosphate co-transporter NaPi-IIc in maintaining phosphate homeostasis. *Am J Hum Genet* 2006;78:178-192.

Lorenz-Deriereux B, Benet-Pages A, Eckstein G et al. Hereditary hypophosphatemic with hypercalciuria is caused by mutations in the sodium/phosphate cotransporter gene SLC34A3. *Am J Hum Genet* 2006; 78:193-201.

Tieder M, Modai D, Samuel R et al. Hereditary hypophosphatemic rickets with hypercalciuria. *New Engl J Med* 1985;312:611-617.

Rizomelic chondrodysplasia punctata

Autosomal recessive (MIM 215100)

RCDP is a rare, multisystem, developmental disorder, characterized by the presence of stippled foci of calcification in hyaline cartilage, coronal vertebral clefting, dwarfing, joint contractures, congenital cataract, ichthyosis, and severe mental retardation. The cataracts are present in about 72% of cases, and skin changes in about 27%. The coronal cleft of the vertebral bodies is demonstrable radiologically and appears to represent embryonic arrest with cartilage occupying the cleft between the anterior and posterior parts of the vertebral bodies. Biochemically, RCDP patients have subnormal levels of red cell plasmalogens and progressive accumulation of phytanic acid starting from normal at birth and increasing to levels more than 10 times normal by age 1 year.

Epidemiology:

The disease has been diagnosed in several patients from a Muslim Arab village in the North of Israel (Mandel H).

Molecular genetics:

Unknown

San Filippo (MPS III)

Autosomal recessive (MIM 252900)

The Sanfilippo syndrome is characterized by severe central nervous system degeneration, but only mild somatic disease. Onset of clinical features usually occurs between 2 and 6 years; severe neurologic degeneration occurs in most patients between 6 and 10 years of age, and death occurs typically during the second or third decade of life. Type A has been reported be the most severe, with earlier onset and rapid progression of symptoms and shorter survival.

The clinical features are severe mental defect with relatively mild somatic features (moderately severe claw hand and visceromegaly, little or no corneal clouding or skeletal, e.g., vertebral, change). The presenting problem may be marked overactivity, destructive tendencies, and other behavioral aberrations in a child of 4 to 6 years of age. The radiologic findings in the skeleton are relatively mild and include persistent biconvexity of the vertebral bodies and very thick calvaria.

The San Filippo syndrome is a lysosomal storage disease due to impaired degradation of heparan sulfate and heparitin sulfate is excreted in the urine. MPS III includes 4 types, each due to the deficiency of a different enzyme: heparan N-sulfatase (type A); alpha-N-acetylglucosaminidase (type B); acetyl CoA: alpha-glucosaminide acetyltransferase (type C); and N-acetylglucosamine 6-sulfatase (type D).

Epidemiology

The disease has been reported in several **Muslim Arab families, in particular in one village.**

Molecular genetics:

N-alpha-acetylglucosaminidase (NAGLU) gene (chromosomal locus 17q21)

The mutation in the patients is [R674H]

N-Sulfoglucosamine sulfohydrolase SGSH (chromosomal locus 17q25.3)

Was reported in several Muslim patients p. L411F, c.416C >T; p.T271M; p.Y89X and one Christian patient p.R233X

Sandoff disease

Autosomal recessive (MIM 268800)

The onset of the symptoms is very similar to Tay Sachs disease around 3-5 months usually manifested with motor weakness. An increased startled reaction to noise is characteristic of these patients. Thereafter there is a progressive deterioration characterized with hypotonia, increased weakness and poor head control. Cherry red spots are typical and the patient's vision diminishes rapidly. After one year of age seizures are common; macrocephaly progressively develop. At the age of 2 years the children are usually essentially in a vegetative state. Death occurs by 2 - 4 years. Several other form of the disease have been reported in particular a juvenile and adult type of the disease.

Epidemiology

The disease has been reported in several **Arab Christian families**.

Molecular genetics:

Beta hexosaminidase gene(chromosomal locus 5)

A patient was homozygous for [IVS8 nt5] that has been reported in a greek cypriot patient

References:

Furihata K, Drousiotou A, Hara Y, Christopoulos G, Stylianidou G, Anastasiadou V, Ueno I, Ioannou P. Novel splice site mutation at IVS8 nt 5 of HEXB responsible for a Greek-Cypriot case of Sandhoff disease. Hum Mutat. 1999;13:38-43.

SERKAL syndrome

Autosomal recessive (MIM)

In 2nd cousin parents of Arab Muslim origin, a child died of hyperammonemia due to citrullinemia type I at age 4 days. Three pregnancies were interrupted because of renal agenesis with a presumptive diagnosis of Potter syndrome. In two of the cases in which details were available, hypoplasia of the adrenal glands was also found. Bilateral cleft lip and palate was diagnosed in two of the fetuses.

Molecular genetics:

WNT4 gene (chromosomal locus 1p35)

The patients were homozygous for [c.C341T] (p.A114V)

References:

Mandel H, Shemer R, Borochowitz ZU, Okopnik M, Knopf C, Indelman M, Drugan A, Tiosano D, Gershoni-Baruch R, Choder M, Sprecher E. SERKAL Syndrome: An Autosomal-Recessive Disorder Caused by a Loss-of-Function Mutation in WNT4. *Am J Hum Genet.* 2008;82:39-47.

Severe combined immune deficiency (SCID)

Omenn syndrome

Autosomal recessive (MIM 202500)

SCID is characterized by high level of genetic and clinical heterogeneity

Infants with autosomal recessive SCID caused by mutations in recombination activating genes 1&2 (RAG1 & RAG2) that are necessary for the somatic rearrangement of antigen receptor genes on T- and B lymphocytes, or in DCLRE1C, resemble all other forms of SCID in their infection susceptibility, however their lymphocyte phenotype is characterized by predominantly circulating NK cells and undetectable B or T lymphocytes (T-B-NK+SCID)

RAG1, RAG2, and DCLRE1C are the primary genes responsible for the T-B-NK+ SCID phenotype. In addition to causing the SCID phenotype, hypomorphic mutations in RAG1 or RAG2 can lead to partially impaired V(D)J recombinational activity resulting in Omenn syndrome (OS). OS can also result from defects in other genes including DCLRE1C, LIG4, IL7RA, common gamma chain AD and CHD7. In OS, the absolute lymphocyte count is elevated due to circulating non-functional oligoclonal T lymphocytes. There is also a third group of patients, called "atypical SCID/OS" or "leaky SCID" patients because the clinical features do not exactly match those of the previous two categories of patients

An autosomal recessive form of SCID has been found in several non-Jewish patients in Israel.

The mutation L454Q in RAG1 was reported in Bedouin families and the mutation C1886T in a Muslim family

References:

Tabori U, Mark Z, Amariglio N, Etzioni A, Golan H, Biloray B, Toren A, Rechavi G, Dalal I. Detection of RAG mutations and prenatal diagnosis in families presenting with either T-B- severe combined immunodeficiency or Omenn's syndrome. Clin Genet. 2004;65:322-326.

Sialic acid storage disease

Autosomal recessive (MIM 269920)

Sialic acid storage diseases are autosomal recessive neurodegenerative disorders that may present as hydrops fetalis, a severe infantile form (ISSD) or as a slowly progressive adult form that is prevalent in Finland (Salla disease). The main symptoms are hypotonia, cerebellar ataxia, and mental retardation; visceromegaly and coarse features are also present in the infantile cases. Progressive cerebellar atrophy and dysmyelination have been documented by magnetic resonance imaging. Enlarged lysosomes are seen on electron microscopic studies, and patients excrete large amounts of free sialic acid in the urine

In the infantile form the main features are coarse facies, hepatosplenomegaly, prominent psychomotor retardation, and unexpectedly fair complexion.

Biochemical analyses of urine and cultured fibroblasts showed increased levels of unbound (free) sialic acid.

Epidemiology

The infantile form of the disease has been diagnosed in two Muslim Arab families from the same town in **Vadi Ara** (Shalev S). Several patients from a **Bedouin** tribe in the Negev were also reported with variable presentation.

Molecular genetics:

SLC17A5 gene (chromosomal locus 6q14-q15)

The Bedouins from the Negev were homozygous for G123A

References:

Landau D, Cohen D, Shalev H, Pinski V, Yerushalmi B, Zeigler M, Birk OS. A novel mutation in the SLC17A5 gene causing both severe and mild phenotypes of free sialic acid storage disease in one inbred Bedouin kindred. *Mol Genet Metab*. 2004;82:167-172.

Sickle cell anemia and other hemoglobinopathies

Autosomal recessive (MIM 141900)

Patients with sickle cell anemia present with variable manifestations of the disease and the more severely affected are those with the Beinin haplotype or compound heterozygotes sickle thalassemia. Because of the high frequency of thalassemia many of the affected patients present with a sickle thalassemia phenotype often more severe than the one of sickle cell anemia.

Sickle cell anemia is relatively frequent among Muslim Arabs in Israel. The disease is found in higher frequency in several villages/towns.

Other hemoglobinopathies have been reported in Israel:

Hemoglobin C disease [$\beta 6 \text{ Glu} \rightarrow \text{Lys}$]. The disease is relatively rare in Israel but several Bedouin patients have been reported from a village in the **Hulah valley**. The presence of hemoglobin C seemed to have no effect on the survival of members of the family.

Hb O Arab [$\beta 121 \text{ Glu} \rightarrow \text{Lys}$]. This hemoglobinopathy is frequent in a village of on the **sea shore**. Within the village beta thalassemia and sickle cell traits are also relatively frequent. The compound heterozygotes HbS/HbO or thalassemia/HbO are moderately affected.

References:

Eliakim E, Rachmilewitz EA. Hemoglobinopathies in Israel. Hemoglobin 1983;4:479-485.

Sjogren-Larsson syndrome

Autosomal recessive (MIM 270200)

The skin changes in Sjogren-Larsson syndrome are similar to those of congenital ichthyosiform erythroderma, although considerable variations in severity have been described. Slight or moderate hyperkeratosis, less pronounced on the face, was already present at birth, but collodion membranes were never seen. Ichthyosis developed to its full extent during infancy. The skin changes were concentrated on the neck and lower abdomen and in the flexures, where the scales were often dark. Hair and nails and ability to sweat were unaffected. Glistening spots in the ocular fundus were an obligatory and early sign. Ecchymoses are present at birth or soon after. The neurologic disorder is described as spastic quadriplegia, most of the patients never walk. Stature tends to be short. About half the patients have seizures. Clinical improvement occurs with fat restriction and supplementation with medium chain triglycerides.

Epidemiology:

The syndrome has been reported in a Muslim Arab family from Jerusalem

Molecular genetics:

fatty aldehyde dehydrogenase (ALDH3A2) gene (chromosomal locus 17p11.2)

In the family from Jerusalem the mutation is 682C>T

References:

Lossos A, Khoury M, Rizzo WB, Gomori JM, Banin E, Zlotogorski A, Jaber S, Abramsky O, Argov Z, Rosenmann H. Phenotypic variability among adult siblings with Sjogren-Larsson syndrome. Arch Neurol. 2006; 63:278-280

SOFT (short stature, onychodysplasia, facial dysmorphism, and hypotrichosis) syndrome

Autosomal recessive (MIM 614813)

The patients presented with disproportionate short stature. The physical examination revealed in addition head circumference that was elevated in early childhood but became markedly low by adulthood, facial dysmorphism including long triangular face with a prominent nose, small ears. Clinodactyly of the fifth finger, brachydactyly, hypoplastic distal phalanges and fingernails. The skeletal findings included short thick long bones with mild irregular changes, short femoral neck and hypoplastic pelvis and sacrum. childhood,

Epidemiology:

The syndrome has been reported several Muslim families from a village in the Galilee

Molecular genetics:

POC1A gene (chromosomal locus 3p21.1-21.31)

In the family from Jerusalem the mutation is c.694-3C>A pLeu171Pro

References:

Sarig O, Nahum S, Rapaport D, Ishida-Yamamoto A, Fuchs-Telem D, Qiaoli L, Cohen-Katsenelson K, Spiegel R, Nussbeck J, Israeli S, Borochowitz ZU, Padalon-Brauch G, Uitto J, Horowitz M, Shalev S, Sprecher E. Short Stature, Onychodysplasia, Facial Dysmorphism, and Hypotrichosis Syndrome Is Caused by a POC1A Mutation. *Am J Hum Genet.* 2012 ;91:337-242.

Smith Lemli Opitz

Autosomal recessive (MIM 270400)

SLOS occurs in relatively high frequency: approximately 1 in 20,000 to 30,000 births in populations of northern and central European background. The major symptoms include 2/3 toe syndactyly; hypospadias; microcephaly; short or proximally placed thumbs; congenital cardiac in particular atrioventricular septal defect present; mental retardation; photosensitivity; abnormal sleep pattern Serum 7-dehydrocholesterol levels are elevated but do not correlate with clinical severity.

Epidemiology:

The syndrome has been diagnosed in several families

Molecular genetics:

sterol delta-7-reductase gene (DHCR (chromosomal location 11q12-q13)

In one Muslim Arab family the mutation was N52S

Spastic paraparesis, vitiligo, premature graying, characteristic facies

Autosomal recessive (MIM 270680)

The disease has been reported in two Arab families in Israel. The affected individuals present with progressive spastic paraparesis with widespread skin pigmentation changes consisting of vitiligo and hyperpigmentation of the exposed area, café au lait and freckles. In one family in addition to the symptoms microcephaly and mental retardation were present.

Epidemiology:

The syndrome has been reported in two families

Molecular genetics:

The locus was mapped to 1q24-q32 in one of the Arab families

References:

- Blumen SC, Bevan S, Abu-Mouch S, Negus D, Kahana M, Inzelberg R, Mazarib A, Mahamid A, Carasso RL, Slor H, Withers D, Nisipeanu P, Navon R, Reid E. A locus for complicated hereditary spastic paraplegia maps to chromosome 1q24-q32. *Ann Neurol*. 2003;54:796-803.
- Lison M, Kornbrut B, Feinstein A, Hiss Y, Boichis H, Goodman RM. Progressive spastic paraparesis, vitiligo, premature graying and distinct facial appearance: a new genetic syndrome in three sibs. *Am J Med Genet* 1981;9:351-357.
- Mukamel M, Weitz R, Metzker A, Varsano I. Spastic paraparesis, mental retardation and cutaneous pigmentation disorder: a new syndrome. *Am J Dis Child* 1985;139:1090-1092.

Spastic paraparesis SPG11

Autosomal recessive (MIM 604360)

The disease was reported in several families. All patients had onset of clinical symptoms during the second decade of life, with cognitive decline preceding gait disturbance by 2 to 5 years. Cardinal signs included pseudobulbar dysarthria, spastic paraparesis with lower limb hyperreflexia, upper limb hyperreflexia, extensor plantar responses, and distal amyotrophy

Molecular genetics:

SPG11 gene (chromosomal locus 15q13-q15)

The mutation Q40X was characterized in one Bedouin family from the Galilee and a mutation c.4339C>T in a Christian Arab family. Two other mutations were reported in Muslim Arabs c.5456delAG; c.2833A>G

References:

Lossos A, Stevanin G, Meiner V, Argov Z, Bouslam N, Newman JP, Gomori JM, Klebe S, Lerer I, Elleuch N, Silverstein S, Durr A, Abramsky O, Ben-Nariah Z, Brice A. Hereditary spastic paraplegia with thin corpus callosum: reduction of the SPG11 interval and evidence for further genetic heterogeneity. *Arch Neurol.* 2006; 63:756-760.

Stevanin G, Santorelli FM, Azzedine H, Coutinho P, Chomilier J, Denora PS, Martin E, Ouvrard-Hernandez AM, Tessa A, Bouslam N, Lossos A, Charles P, Loureiro JL, Elleuch N, Confavreux C, Cruz VT, Ruberg M, Leguern E, Grid D, Tazir M, Fontaine B, Filla A, Bertini E, Durr A, Brice A. Mutations in SPG11, encoding spatacsin, are a major cause of spastic paraplegia with thin corpus callosum. *Nat Genet.* 2007;39:366-372.

Spinal muscular atrophy

Autosomal recessive (MIM 253300)

Spinal muscular dystrophy (SMA) is a neuromuscular disorder caused by the degeneration of the anterior neuron horn cells of the spinal cord which result in symmetric proximal muscle weakness. Patients with SMA are classified in three groups according to the age at onset and maximum motor function. Type I is the most severe form of the disorder with onset at less than 6 months of age inability to sit or walk and death before the age of 2 years.

The molecular basis for the disorder is in most cases a deletion of the gene SMN1.

Epidemiology:

The disorder has been diagnosed in several Arab families in Israel, in particular in a village on the Mediterranean coast. The disease represents one of the major monogenic cause of infant mortality among Arabs in Israel.

Molecular genetics:

Survival motor neurone 1 SMN1 (chromosomal locus 5q21.2-q13.3)

Spinocerebellar degeneration with slow eye movements

Autosomal recessive (MIM 271322)

In an Arab family of Palestinian origin from Kuwait an autosomal recessive form of spinocerebellar degeneration with slow eye movements was reported. Associated features included progressive intellectual impairment and extrapyramidal dysfunction as well as peripheral neuropathy and skeletal abnormalities. Muscle biopsy showed nonspecific mitochondrial abnormalities. The pedigree showed 3 affected males and 3 affected females in 2 sibships, both with consanguineous parents and at least one common ancestral couple. The progress of the disorder was slow and a severe disability was reached in 10-15 years, but even at that stage the main disability was that of gait and patients managed to live with minimal help except for walking.

Epidemiology:

The syndrome has been reported in a single family.

Molecular genetics:

Unknown

References:

Al-Din ASN, Al-Kurdi A, Al-Salem MK, Al-Nassar KE, Al-Zuhair A, Rudwan MA, Ayish I, Barghouti JA, Khaffaji S, Hamawi T. Autosomal recessive ataxia, slow eye movements, dementia and extrapyramidal disturbances. *J. Neurol Sci* 1990;96:191-205.

Spondylocostal dysostosis

Autosomal recessive (MIM 277300)

Spondylocostal dysostosis is the association of multiple vertebral segmentation defects with rib anomalies. It is a short stature short trunk syndrome with non-progressive kyphoscoliosis and radiological appearances of a variable degree of multiple hemivertebrae. The involvement of the thoracic spine lead to irregular rib alignment and points of fusion and occasionally ribs are absent.

Epidemiology:

The syndrome has been diagnosed in 6 individuals from a large kindred living in the **Galilee**. In the kindred most of the affected males have in addition to the skeletal defects inguinal hernias which required.

Molecular genetics:

Human homologue of DLL3 (chromosomal locus 19q13.1-q13.3).

The mutation responsible for the disease in the kindred is in exon 5: [S198ins5] and all the patients are homozygous.

References:

Bulman MP, Kusumi KM, Frayling TM, McKeown C, Garret C, Lander ES, Krumlauf R, Hattersley T, Turpenny PD. Mutations in the human delta homologue DLL3 cause axial skeletal defects and spondylocostal dysostosis. *Nature Genet* 2000; 24:438-441.
 Turnpenny PD, Thwaites RJ, Boulos FN. Evidence for variable gene expression in a large kindred with autosomal recessive spondylocostal dysostosis. *J Med Genet* 1991;28:27-33.

Spondylo-epi-metaphyseal dysplasia (SEMD) matrilin 3 type

Autosomal recessive (MIM 608728)

The spondyloepimetaphyseal dysplasias (SEMDs) are a heterogeneous group of skeletal disorders characterized by defective growth and modeling of the spine and long bones. The SEMDs are distinguished from the spondylometaphyseal dysplasias (SMDs) and the spondyloepiphyseal dysplasias (SEDs) by the combined involvement of the epiphyses and metaphyses. The 3 disorders--SEDs, SMDs, and SEMDs--have malformations of the vertebrae in common. The SEMDs often occur as isolated cases, but distinctive heritable forms with autosomal dominant inheritance, X-linked inheritance, and autosomal recessive inheritance have been reported.

A large consanguineous family with a novel form of autosomal recessive SEMD was reported in which affected individuals presented with disproportionate early onset dwarfism bowing of lower limbs lordosis and normal hands.

Molecular genetics:

Matrilin 3 MATN3 gene chromosomal locus 2p23-p24

All the affected in the pedigree were homozygous 973T>A

References:

Borochowitz ZU, Scheffer D, Adir V, Dagoneau N, Munnich A, Cormier-Daire V. Spondylo-epi-metaphyseal dysplasia (SEMD) matrilin 3 type: homozygote matrilin 3 mutation in a novel form of SEMD. J Med Genet 2004;41:366-372.

Spondylo-meta-epiphyseal dysplasia (SMED)

Autosomal recessive (MIM 271665)

The disorder was first reported by Borochowitz et al. including disproportionate short stature, platyspondyly; abnormal epiphyses and metaphyses; shortening of the lower and upper limbs; short, broad fingers; and premature calcifications. The dysplasia is progressive with respect to the severity of the bowing of the lower limbs and to the appearance of the calcifications. The chondral calcifications appear in childhood and become more severe with age.

Epidemiology:

The syndrome has been diagnosed in 5 Muslim Arab families from Jerusalem

Molecular genetics:

DDR2 gene (chromosomal locus 1q23)

All Muslim Arabs from Jerusalem were homozygous c.2254 C>T [R752C]

References:

- Borochowitz Z, Langer LO Jr, Gruber HE, Lachman R, Katznelson MB, Rimoin DL. Spondylo-meta-epiphyseal dysplasia (SMED), short limb-hand type: a congenital familial skeletal dysplasia with distinctive features and histopathology. *Am J Med Genet* 1993 45:320-326.
- Bargal R, Cormier-Daire V, Ben-Neriah Z, Le Merrer M, Sosna J, Melki J, Zangen DH, Smithson SF, Borochowitz Z, Belostotsky R, Raas-Rothschild A. Mutations in *DDR2* Gene Cause SMED with Short Limbs and Abnormal Calcifications. *Am J Hum Genet* 2009;84:80-84.

Stuve-Wiedmann syndrome

Autosomal recessive (MIM 601559)

The patients have feeding and swallowing difficulties, respiratory insufficiency, abnormal appearance, muscle hypotonia, and postnatal short stature. The syndrome is typically lethal in the neonatal period. Recurrent episodes of unexplained fever were the cause of death in most of patients.

Clinical features include camptodactyly with ulnar deviation. Contractures of the elbows and fingers are observed as well as congenital bowing of the long bones and short stature. Radiographically the long bones are short and thick with large metaphyses.

Epidemiology

The disorder was described in three Palestinian families from the **region of Jerusalem**.

Molecular genetics

Null Leukemia Inhibitory Factor Receptor (LIFR) gene (chromosomal locus 5p13.1)

Among the two patients examined two different mutations were found each in homozygosity: 1601-G-A and 2472-2476delTATGT.

References

- Dagoneau N, Scheffer D, Huber C, Al-Gazali LI, Di Rocco M, Godard A, Martinovic J, Raas-Rothschild A, Sigaudy S, Unger S, Nicole S, Fontaine B, Taupin JL, Moreau JF, Superti-Furga A, Le Merrer M, Bonaventure J, Munnich A, Legeai-Mallet L, Cormier-Daire V. Null Leukemia Inhibitory Factor Receptor (LIFR) Mutations in Stuve-Wiedemann/Schwartz-Jampel Type 2 Syndrome. *Am J Hum Genet.* 2004;74:298-305.
- Raas-Rothschild A, Ergaz-Schaltiel Z, Bar-Ziv J, Rein AJ. Cardiovascular abnormalities associated with the Stuve-Wiedemann syndrome. *Am J Med Genet.* 2003; 121A:156-158.

Symphalangism with multiple anomalies of hand and feet

Autosomal dominant (MIM 185750)

The father and 5 of his 11 children had proximal symphalangism with syndactyly, clinodactyly, hypoplasia of the thenar and hypothenar eminences, and a distinctive dermatoglyphic pattern. All the features showed considerable variability. No linkage was demonstrated with the marker traits studied.

Epidemiology:

The syndrome has been reported in a single family

Molecular genetics:

Unknown

References:

Learman Y, Katznelson M, Bonne-Tamir B, Engel J, Hertz M, Goodman RM.
Symphalangism with multiple anomalies of the hands and feet: a new genetic trait. Am J Med Genet 1981;10:245-255.

Tay Sachs disease

Autosomal recessive (MIM 271800)

The onset of the symptoms in the infantile Tay Sachs disease is around 3-5 months usually manifested with motor weakness. An increased startled reaction to noise is characteristic of these patients. Thereafter there is a progressive deterioration characterized with hypotonia, increased weakness and poor head control. Cherry red spots are typical and the patient's vision diminishes rapidly. After one year of age seizures are common; macrocephaly progressively develop. At the age of 2 years the children are usually essentially in a vegetative state. Death occurs by 2 - 4 years. Several other form of the disease have been reported in particular a juvenile and adult type of the disease.

Epidemiology and molecular genetics:

The disease has been diagnosed in at least two non-Jewish families in Israel. In one Muslim Arab family the patient was homozygous for a stop codon mutation in Tyr 26 (G to a transition 78). In a Druze patient born to first cousin parents, the child was affected with a late infantile disease and was found to be compound heterozygote. One allele included two adjacent mutations in exon 5[Δ496C] resulting in a frame shift and a silent mutation [498C→G]. In the other allele the mutation was [S279P].

References:

- Drucker L, Navon R. Tay Sachs disease in an Israeli Arab family. *Human Mut* 1993 2:415-417.
- Drucker L, Hemli JA, Navon R. Two mutated HEXA alleles in a Druze patient with late infantile Tay Sachs. *Hum Mut* 1997; 10:451-457.

Tetra-amelia with multiple malformations (Zimmer syndrome)

Autosomal recessive (MIM 301090)

The syndrome was first reported in several males in a large Arab kindred. All the patients had tetra amelia with very severe malformations including absence of nose, eyes, ears, cleft of the lips. In addition at least one patient affected with a similar syndrome had also a female karyotype with a male external genitalia. The affected either die at birth or during pregnancy. The syndrome was reported with probable X linked inheritance however, it seems that ambiguous genitalia may be part of the syndrome and explain the male limitation of an autosomal recessive syndrome. It may be that it represent a severe form of the syndrome of tetra-amelia with pulmonary hypoplasia (MIM 273395).

Epidemiology:

The syndrome has been reported in a single kindred.

Molecular genetics:

Unknown

References:

- Gershoni-Baruch R, Drugan R, Bronstein, Zimmer EZ. Zimmer syndrome or X-linked amelia? *Am J Med Genet* 1990 37:569-572.
- Kosaki K, Jone MC, Stayblot. Zimmer phocomelia: delineation by principal coordinate analysis. *Am J Med Genet* 1996; 66:55-59.

Tetra-amelia with pulmonary hypoplasia

Autosomal recessive (MIM 273395)

All the affected have severe limb defects including either complete amelia or phocomelia. In addition in some cases other malformations were present such as cleft lip and hydrocephalus. The affected either die soon after birth because of pulmonary hypoplasia or are diagnosed during the pregnancy which may be interrupted because the severe limb defects. It may be that the syndrome represents a milder form of the tetra-amelia syndrome with multiple malformations (MIM 301090, Zimmer syndrome).

Epidemiology:

All the patients reported were from unrelated Muslim Arab families from the **region of Jerusalem/Hebron**.

Molecular genetics:

Unknown

References:

Rosenak D, Ariel I, Arnon J, Diamant YZ, Ben Chetrit A, Nadjari M, Zilberman R, Yaffe H, Cohen T, Ornoy A . Recurrent tetraamelia and pulmonary hypoplasia with multiple malformations in sibs. *Am J Med Genet* 1991; 38: 25-28.

Zlotogora J, Sagi M, Shabany YO, Jarallah RY. Syndrome of tetraamelia with pulmonary hypoplasia. (Letter) *Am J Med Genet* 1993;47:570-571.

TGB deficiency

X linked recessive (MIM 314200)

Mutations at the TGB locus leading to reduced thyroxine binding globulin are euthyroid. In rule they are discovered through thyroid function examinations.

Epidemiology:

In Israel, the disorder is frequent in a Muslim Arab village near the coast (Zak, personal communication) and among the Bedouin of the Negev.

Because of the high degree of inbreeding homozygous female patients, have been found.

Molecular genetics:

Among the Bedouin of the Negev, a complete TGB deficiency was found in 8 subjects (7 males and one female) from 2 different tribes. The molecular studies demonstrated a deletion in codon 38 in exon 1 leading to a truncation of the TGB protein. The female patient was homozygous for the mutation

References.

Miura Y, HersHKovitz E, Inagaki A, Parvari R, Oiso Y, Phillip M. A novel mutation causing complete thyroxine binding globulin deficiency (TGB-CD-Negev) among the Bedouin in Southern Israel. *J Clin Endocrin Metab* 2000;85:3687-3689.

Thalassemia, alpha and alpha hemoglobinopathies

Autosomal recessive (MIM 141850)

Mutations in the alpha globin genes have been found among Arabs in Israel including large rearrangements of the alpha gene, triplication of the alpha genes and the alpha Mediterranean deletion. In addition several point mutations were reported in particular Hemoglobin Taybe [alpha 1, Δ T39], [alpha 2 IVS1 nt Δ 5] and [alpha 2 poly A nt 6 A→G].

Several patients have been reported from the town of **Taybe** and were affected with moderate hemolytic anemia. Homozygosity produce a severe defect, even hydrops fetalis

References:

- Arnon S, Tamary H, Dgany O, Litmanovitz I, Regev R, Bauer S, Dolfen T, Yacobovich J, Wolach B, Jaber L. Hydrops fetalis associated with homozygosity for hemoglobin Taybe (alpha 38/39 THR deletion) in newborn triplets. *Am J Hematol.* 2004 ;76:263-266.
- Ben Bassat, Jaber L. Hb Taybe: description of genetics and laboratory findings in an Israel Arab family. *Hemoglobin* 1998;22:161-166.
- Eliakim E, Rachmilewitz EA. Hemoglobinopathies in Israel. *Hemoglobin* 1983;4:479-485.
- Galacteros F, Girodon E, M'Rad A, Martin J, Goossens M, Jaber L, Cohen JJ, Tamary H, Goshen Y, Zaizov R, et al. Hb Taybe (alpha 38 or 39 THR deleted): an alpha-globin defect, silent in the heterozygous state and producing severe hemolytic anemia in the homozygous. *C R Acad Sci III.* 1994;317:437-444.
- Oron-Karni V, Filon D, Shifrin Y, Fried E, Pogrebijsky, Oppenheim A, Rund D. Diversity of alpha globin mutations and clinical presentation of alpha thalassemia in Israel. *Am J Hemat* 2000;65:196-203.

Thalassemia, Beta

Autosomal recessive (MIM 141900)

The clinical manifestations are the result of the deficient synthesis of β globin chains, which can be either total or partial and hence the manifestations of the disease range from the severe to milder cases. The severely affected are known as thalassemia major and they usually do not synthesize any β globin chains and are also referred as β thalassemia. The less severely affected are called thalassemia intermedia and usually show synthesis of some β globin chains. Heterozygotes are known as thalassemia minor since they present with a very mild anemia. The severe form is characterized by a severe anemia which usually is present from the second half of the first year of life. If untreated by adequate blood transfusions the hemoglobin levels are extremely low and the growth of the child is severely retarded and skeletal changes caused by the expansion of the bone marrow lead to the typical facial appearance. Huge splenomegaly develop leading to hypersplenism. Leg ulcers and gallstones may be found. Treated patients present with late complications of iron deposition in particular hepatic and cardiac. Therefore the treatment should include in addition to frequent blood transfusions iron chelating agents to prevent these complications. Bone marrow transplantation when successful is a cure for these patients.

The clinical picture is milder in thalassemia intermedia as seen by the number and frequency of blood transfusions needed to maintain adequate levels of hemoglobin. The diagnosis is clinical together with the characteristic hematological characteristic findings which include microcytic anemia with a typical blood smear, elevated levels of hemoglobin F and often A₂. In heterozygotes a mild microcytic anemia with typical indices and usually elevated hemoglobin A₂.

The carrier frequency of beta thalassemia among Arabs is estimated to be 10% the disease may be less frequent among Christian than among Muslim Arab, and the carrier frequency among Druze is probably also lower.

A total of 17 different mutations in the β globin gene have been identified among Arabs in Israel. The most prevalent mutation is the common Mediterranean allele IVS1-110 but it is responsible only for 27% of the Arab alleles while in the region it represent 42% of the alleles in Turkey, 62% in Lebanon and 41% in Egypt. The N37 mutation was identified in 8% of all the Arab mutant alleles, while it is very rare in other populations. Other relatively frequent mutations are IVS1-6, IVS1-1, and FS8. The mutation IVS2-745 was found only in a discrete location near Nazareth in several families and IVS1-5 in several villages in the region of Jerusalem. The uncommon mutation IVS 2-1, was found only among Druze.

References:

Filon D, Oron V, Krichevski S, Shaag A, Shaag Y, Warren TC, Goldfarb A, Shneor Y, Koren A, Aker M, Abramov A, Rachmilewitz E, Rund D, Kazazian HH Jr, Oppenheim A. Diversity of β globin mutations in Israeli ethnic groups reflects recent historic events. *Am J Hum Genet* 1994;54:836-843.

Thiamine responsive megaloblastic anemia

Autosomal recessive (MIM 249270)

The disease is characterized by a triad of megaloblastic anemia, diabetes mellitus non type I and sensorineural deafness. In addition, some patients have also congenital heart abnormalities, heart arrhythmias, and abnormalities of the retina and the optic nerve. The disease is characterized by a state of thiamine deficiency and the administration of high doses causes the reversal to varying degrees of most of the clinical features.

Epidemiology:

The disease has been diagnosed among Muslim Arabs **in two villages in the Galilee**.

Molecular genetics:

SLC19A2 gene encoding a thiamine transporter (chromosomal locus 1q23.2-1q23.3).

The same mutation in SLC19A2 [del242fs/ter259] has been demonstrated in all the patients. The same mutation was also found in a Lebanese patient and all the affected share a same haplotype. Therefore, these Arab families probably share a common ancestor

References:

- Labay V, Raz T, Baron D, Mandel H, Williams H et al. Mutations in SLC19A2 cause thiamine responsive megaloblastic anemia associated with diabetes mellitus and deafness. *Nature Genet* 1999; 22:300-304.
- Mandel H, Berant M, Hazani A, Naveh Y. Thiamine dependent beriberi in the thiamine responsive anemia syndrome. *New Engl J Med* 1984;311:836-838.
- Raz T, Barret T, Szargel R, Mandel H, Neufeld EJ et al. Refined mapping of the gene for thiamine responsive megaloblastic anemia and evidence for genetic homogeneity. *Hum Genet* 1998;103:455-461.

Thrombastenia of Glanzmann

Autosomal recessive (MIM 273800)

Glanzmann thrombasthenia is a disorder of platelet function manifested by severe bleeding tendency. All post puberty females suffers from menorrhagia. Purpura epistaxis and gingival bleeding are observed in more than 70% of the patients. Approximately 50% of the patients suffer from gastrointestinal bleeding. Because of possible bleeding during surgery these patients must receive platelets transfusion before the procedure.

All the patients have a prolonged bleeding time, an absent clot retraction during 60mm incubation at 37 degrees. The platelets may be seen on a blood smear prepared without an anticoagulant and the platelet count is normal.

The biochemical basis of the disease is a deficiency or an abnormal structure of the platelet glycoprotein IIb/IIIa complex.

Epidemiology:

The syndrome has been reported in several families.

Molecular genetics:

Glycoprotein IIb or IIIa genes.

The disease is caused by mutations in either glycoprotein IIb or IIIa genes. A same 13 bp deletion IVS4-3, at the AG acceptor splice site of exon 4 on the glycoprotein IIb ITGA2b gene is a founder mutation in the Palestinian population.

In one family the patients were homozygous for A97G in alphaIIb gene

References:

- Mansour W, Einav Y, Hauschner H, Koren A, Seligsohn U, Rosenberg N. An α IIb mutation in patients with Glanzmann thrombasthenia located in the N-terminus of blade 1 of the β -propeller (Asn2Asp) disrupts a calcium binding site in blade 6. *J Thromb Haemost.* 2011 ;9:192-200
- Peretz H, Seligsohn U, Zwang E, Coller BS, Newman PJ. Detection of the Glanzman's thrombasthenia mutations in Arab and Iraqi-Jewish patients by polymerase chain reaction and restriction analysis of blood and urine samples. *Thromb Haemost* 1991; 66:500-504.
- Rosenberg N, Hauschner H, Peretz H, Mor-Cohen R, Landau M, Shenkman B, Kenet G, Coller BS, Awidi AA, Seligsohn U. A 13-bp deletion in alpha gene is a founder mutation that predominates in Palestinian-Arab patients with Glanzmann thrombasthenia. *J Thromb Haemost.* 2005; 3:2764-2772.

Trigonobrachycephaly, bulbous bifid nose, micrognathia and abnormalities of the hands and feet

Autosomal recessive (MIM 275595)

A brother and sister, offspring of healthy first-cousin Palestinian Arab parents, were reported by Teebi, who had trigonocephaly, brachycephaly, bulbous nose which was slightly bifid at the tip, micrognathia, and relatively broad metatarsals and phalanges. Both showed severe psychomotor retardation. The metopic sutures were prominent and the forehead narrow.

Epidemiology:

The syndrome has been reported in a single family

Molecular genetics:

Unknown

References:

Teebi AS. Trigonobrachycephaly, bulbous bifid nose, macrostomia, micrognathia, acral anomalies, and hypotonia in sibs. *Am J Med Genet* 1991;38:529-531.

Trigonomegaly with mental retardation dwarfism and pigmentary degeneration of retina.

Autosomal recessive (MIM 275400)

In an Israeli Muslim Arab family a brother and sister with retinitis pigmentosa, growth failure, long eyelashes, and sparse hair. They were born to young healthy consanguineous parents and presented at birth with IUGR. Evolving pigmentary retinopathy was diagnosed at the age of 5 years.

References

Haimi M, Gershoni-Baruch R Autosomal recessive Oliver-McFarlane syndrome: retinitis pigmentosa, short stature (GH deficiency), trichomegaly, and hair anomalies or CPD syndrome (chorioretinopathy-pituitary dysfunction). *Am J Med Genet A* 2005;138:268-271.

Tyrosinemia type II (oculocutaneous tyrosinaemia type II or Richner-Hanhart syndrome)

Autosomal recessive USH1B (MIM 276600)

Deficiency of the hepatic cytosolic enzyme tyrosine aminotransferase (TAT) causes marked hypertyrosinaemia leading to painful palmoplantar hyperkeratoses, pseudodendritic keratitis and variable mental retardation.

Epidemiology:

The disease has been reported in several Muslim Arab families.

Molecular genetics:

TAT gene (chromosomal locus 16q22)

Two mutations were reported [p.T408] and[R417X]

References:

Maydan G, Andresen BS, Madsen PP, Zeigler M, Raas-Rothschild A, Zlotogorski A, Gutman A, Korman SH. TAT gene mutation analysis in three Palestinian kindreds with oculocutaneous tyrosinaemia type II; characterization of a silent exonic transversion that causes complete missplicing by exon 11 skipping. *J Inher Metab Dis.* 2006;29:620-626.

Ulnar hypoplasia with mental retardation

Autosomal recessive (MIM 276821)

The association of mesomelic shortness of the upper limbs (mainly due to hypoplastic ulna), clubfeet, and absence of fingernails was described by Kohn et al in 2 males born of an inbred Arab couple from the **Gaza strip**. Lower limbs showed limitation of movement at the knees, severe varus deformity, and absence of all toenails. The arms showed limitation of movement at the elbows and absence of all fingernails. One child, who was severely mentally retarded, died at the age of 3 years; the other child died at age 6 months. Ultrasound examination during the next pregnancy revealed a fetus with bilaterally short forearms. The pregnancy was terminated, and a female fetus with similar malformations was delivered. Autopsy showed no internal anomalies.

Epidemiology:

The syndrome has been reported in a single family

Molecular genetics:

Unknown

References:

Kohn G, Malinger G, El Shawwa R, Scheinfeld A, Tepper R, Ornoy A, Lachman R, Rimoin DL. Bilateral ulna hypoplasia, club feet, and mental retardation: a new mesomelic syndrome. *Am J Med Genet* 1995;56:132-135.

Usher syndrome

Autosomal recessive USH1B (MIM 276903)

The Usher syndromes are a group of diseases which associate retinitis pigmentosa and sensorineural deafness. Variation in the severity of the hearing loss and vestibular response among affected families distinguish between three different genotypes Usher type 1 (USH1), type 2 (USH2) and type 3 (USH3). Genetic heterogeneity was demonstrated and at least 5 different loci for USH1 are known; the most frequent is USH1B accounting for 70% of these patients.

Usher syndrome type I is characterized by congenital, bilateral, profound sensorineural hearing loss. Patients do not develop speech. All patients have vestibular areflexia. retinitis pigmentosa, a progressive, bilateral, symmetrical degeneration of rod and cone functions of the retina, develops in adolescence, resulting in progressively constricted visual fields and impaired visual acuity.

Epidemiology:

The syndrome is frequent among **Samaritans** a small community with a very high consanguinity rate. The syndrome has been also diagnosed in several non-Jewish families in Israel.

Molecular genetics:

Mutations in genes at six different loci cause Usher syndrome type I

MYO7A (chromosomal locus 11q13.5)

In one of the lineages of the Samaritans the disease is due to a stop codon mutation in MYO7A.

References:

Bonne Tamir B, Nystuen A, Seroussi E, Kalinsky H, Kwitek-Black AE et al. Usher syndrome in the Samaritans strengths and limitations of using inbred populations to identify. Am J Phys Anthropol 1997;104:193-200.

Ventricular tachycardia, polymorphic catecholaminergic

Autosomal recessive (MIM 604772)

Catecholaminergic polymorphic ventricular tachycardia (PVT) is characterized by episodes of syncope, seizures, or sudden death in response to physiological or emotional stress. In a Bedouin tribe, from the North of Israel 9 children (age, 7+/-4 years) from 7 related families have died suddenly, and 12 other children suffered from recurrent syncope and seizures starting at the age of 6+/-3 years. Parents of affected individuals were asymptomatic and were all related (first-, second-, or third-degree cousins). Segregation analysis suggested autosomal recessive inheritance. All 12 symptomatic patients and 1 asymptomatic sibling (mean age, 13+/-7 years) were found to have a relative resting bradycardia (64+/-13 bpm, versus 93+/-12 bpm in the unaffected siblings), as well as PVT induced by treadmill or isoproterenol infusion and appearing at a mean sinus rate of 110+/-10 bpm. Patients responded favorably to treatment with beta-blockers.

Epidemiology:

A **Bedouin tribe**, from the North of Israel

Molecular genetics

Calsequestrin 2 gene CASQ 2.(chromosomal locus 1p13-21)

All the patients from the Bedouin tribe are homozygous for the same mutation [D307H], a G→C non synonymous substitution at nucleotide 1038 (exon 9)

References:

Lahat H, Pras E, Olender T, Avidan N, Ben-Asher E, Man O, Levy-Nissenbaum E, Khoury A, Lorber A, Goldman B, Lancet D, Eldar M. A Missense Mutation in a Highly Conserved Region of *CASQ2* Is Associated with Autosomal Recessive Catecholamine-Induced Polymorphic Ventricular Tachycardia in Bedouin Families from Israel. *Am J Hum Genet* 2001; 69:1378-1384..

Von Willebrand type III

Autosomal recessive (MIM 193400)

Major clinical problems are gastrointestinal, urinary, and uterine bleeding; hemarthroses were rare. The condition ameliorated with age.

The platelet is intrinsically normal but has reduced adhesiveness because of factor VIII deficiency, and the plasma from persons with classic hemophilia will correct both the vascular defect and the factor VIII deficiency.

At least 2 biochemical steps are involved in the synthesis of antihemophilic globulin . The first step, under control of an autosomal locus, produces the von Willebrand factor which is concerned with platelet adhesiveness and therefore with vascular integrity. The von Willebrand factor is also the substrate for the second step which is under X-chromosome control and which results in AHG.

Epidemiology:

Von Willibrand type III has been diagnosed in several Arab families in Israel.

Molecular genetics

VWF gene (chromosomal locus 12p13.3)

References:

Berliner SA, Seligsohn U, Zivelin A, Zwang E. A relatively high frequency of severe (type III) von Willibrand disease in Israel. Br J Hemat 1986; 62 535-543.

Waardenburg syndrome

Autosomal dominant (MIM 193500)

Waardenburg syndrome is variable and includes different types. The characteristic feature in WSI is the increased intercanthal distance. Other features include deafness and pigmentary defect (heterochromia, white lock).

Epidemiology:

In a very large kindred many affected individuals were diagnosed. Because of the high degree of inbreeding several homozygotes for WS1 were born in the kindred.

Molecular genetics

PAX 3 gene (chromosomal locus 2q35)

A single mutation S84F was demonstrated in all the affected and was in homozygosity in one patient severely affected.

References:

Zlotogora J, Lerrer I, Ben David S, Ergaz Z, Abeliovich D. Homozygosity for Waardenburg syndrome. Am J Hum Genet 1995;56:1173-1178.

Walker-Warburg syndrome

Autosomal recessive (MIM 236670)

The association of hydrocephalus with retinal dysplasia has been reported in several patients and later a syndrome was delineated which includes central nervous system malformations with dilated thin cortex and lissencephaly type II and encephalocele has been reported in several cases. The eye abnormalities were first reported as retinal detachment but includes microphthalmia, cataract, immature anterior chamber angle and retinal dysplasia with or without detachment. In addition, congenital muscular dystrophy is present as demonstrated by pathology.

Epidemiology:

The syndrome has been diagnosed in many non Jewish families from Israel in particular the region of **Jerusalem/Hebron** and in the Galilee.

Molecular genetics:

Several genes have been reported to be responsible for the syndrome

POMT1 gene (chromosomal locus 9q34.1)

An homozygous patient with [c.1260_1261delCT](p.L421fs) has been reported.

POMT2 gene (chromosomal locus 14q24.3)

An homozygous patient with [c.924-2A>C](p.K307fs) has been reported.

References:

Manzini MC, Gleason D, Chang BS, Hill RS, Barry B, Partlow JN, Poduri A, Currier S, Galvin-Parton P, Shapiro LR, Schmidt K, Davis JG., Basel-Vanagaite L. Seidahmed MZ, Salih MAM, Dobyns WB., Walsh CA. Ethnically diverse causes of Walker-Warburg syndrome (WWS): FCMD mutations are a more common cause of WWS outside of the Middle East. Human Mutation 2008 ;29:E231-41.
Zlotogora J. Genetic disorders among the Palestinian Arabs. 2: neural tube defects and hydrocephalus. Am J Med Genet 1997; 71:33-35.

Warburg microsyndrome

Autosomal recessive (MIM 600118)

The syndrome is characterized by microcephaly, mental retardation, corpus callosum hypoplasia congenital cataracts, microcornea, microphthalmia, progressive joint contractures with failure to thrive and hypothalamic hypogonadism.

Epidemiology:

The disease has been reported in two Muslim families one from Jerusalem the other from the Galilee.

Molecular genetics:

RAB3GAP1 (chromosomal locus 2q21.3)

The syndrome is variable and in one family from the region of Jerusalem the affected children were very severely retarded and handicapped the mutation was c.1786_1789delAAAG (p.Lys596GlufsX613). In another family the patients were mildly affected with the main symptoms of congenital cataracts and hypogonadism with mild mental retardation. The mutation in this family was c.2386G>A p.E796K (Shalev personal communication).

References:

Morris-Rosendahl DJ, Segel R, Born AP, Conrad C, Loeys B, Brooks SS, Müller L, Zeschnigk C, Botti C, Rabinowitz R, Uyanik G, Crocq MA, Kraus U, Degen I, Faes F. New RAB3GAP1 mutations in patients with Warburg Micro Syndrome from different ethnic backgrounds and a possible founder effect in the Danish. *Eur J Hum Genet.* 2010; 8:1100-1106.

Weissenbacher-Zweymuller syndrome

Autosomal recessive (MIM 277610)

The disorder is caused by mutation in the COL11A2 gene and is allelic to otospondylomegaepiphyseal dysplasia; OSMED and the nonocular Stickler syndrome (Stickler syndrome type III).

Epidemiology:

The disease has been reported in a Bedouin family from the Negev

Molecular genetics:

COL11A2 gene (chromosomal locus 6p21.3)

The bedouin patients are homozygous for [R845X].

References:

Harel T, Rabinowitz R, Hendler N, Galil A, Flusser H, Chemke J, Gradstein L, Lifshitz T, Ofir R, Elbedour K, Birk OS. COL11A2 mutation associated with autosomal recessive Weissenbacher-Zweymuller syndrome: Molecular and clinical overlap with otospondylomegaepiphyseal dysplasia (OSMED). Am J Med Genet. 2005;132A 33-35.

Wilson disease

Autosomal recessive (MIM 27900)

Wilson disease is a disorder of copper metabolism that can present with hepatic, neurological, or psychiatric disturbances, or a combination of these, in individuals ranging in age from three years to over 50 years. The following types of liver disease can be observed: recurrent jaundice, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, fulminant hepatic failure, or chronic liver disease.

Neurological presentations include movement disorders (tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement). Psychiatric disturbance includes depression, neurotic behaviors, disorganization of personality, and, occasionally, intellectual deterioration. Treatment with copper chelating agents or zinc can prevent the development of hepatic, neurologic, and psychiatric findings in asymptomatic affected individuals and can reduce findings in many symptomatic patients.

Diagnosis depends upon the detection of low serum copper and ceruloplasmin concentrations and increased urinary copper excretion.

Epidemiology:

The incidence of Wilson disease was calculated in the different Israeli communities in 1984 and was 1:10,000 among Arabs and 1:3,000 among Druze.

Molecular genetics:

ATP7B gene (chromosomal locus 13q14-q21)

At least 5 families are known among the Druze patients and the mutation [3648del6] was characterized while at least another mutation is not yet identified. Similarly among Arabs 8 families are known and one mutation [1639delC] was characterized and at least one other exist.

References:

- Bonne-Tamir B, Frydman M, Agger MS, Bekeer R, Bowcock AM, Hebert JM, Cavalli-Sforza LL, Farrer LA. Wilson's disease in Israel: a genetic and epidemiological study. *Ann Hum Genet* 1990; 54 155-165.
- Kalinsky H, Funes A, Zedlin A, Pel-Or Y, Korotishevsky M, Gershoni-Baruch R, Farrer LA, Bonne-Tamir B. Novel ATP7B mutations causing Wilson disease in several Israeli ethnic groups. *Hum Mut* 1998;11 145-151

Wolman disease

Autosomal recessive (MIM 278000)

The involvement of the viscera is an important feature and death occurred at the age of about 3 months. The major clinical features are vomiting, diarrhea with steatorrhea. Vomiting hepato- splenomegaly is diagnosed early with hepatic fibrosis and often esophageal varices. Nutritional failure is evident.

The disease is due to the deficiency of the lysosomal acid lipase A.

Epidemiology:

The syndrome has been diagnosed in several families and is aparticularly frequent in one village (Gershoni-Baruch R) (carrier rate 1:28).

Molecular genetics:

LIPA gene (chromosomal locus 10q24-q25)

In two of the Muslim Arab families from different villages in the Galilee the patients were homozygous for the same mutation [S106X].

References:

Zschenker O, Jung N, Reithmeier J, Trautwein S, Hertel S, Zeigler M, Ameis D. Characterization of lysosomal acid lipase mutations in the signal peptide and mature polypeptide region causing Wolman disease. J Lipid Res 2001;42:1033-1040.

Woodhouse-Sakati syndrome

Autosomal recessive (MIM241080)

The syndrome includes the combination of hypogonadism, partial alopecia, diabetes mellitus and variable degree of mental retardation.

Epidemiology:

The syndrome has been diagnosed in two Bedouin families in the center of Israel.

Molecular genetics:

C2ORF37 gene (chromosomal locus 2q22.3-q35)

The patients were homozygous for the same mutation [c.436delC] that was found as the founder mutation among the Bedouins from Saudi Arabia.

References:

Rachmiel M, Bistrizter T, Hershkoviz E, Khahil A, Epstein O, Parvari R. Woodhouse-Sakati Syndrome in an Israeli-Arab Family Presenting with Youth-Onset Diabetes Mellitus and Delayed Puberty. *Horm Res Paediatr.* 2011;75:362-366

Xanthinuria

Autosomal recessive (MIM 603592)

Classical xanthinuria is a rare disorder characterized by excessive excretion of xanthine in urine. Type I disease results from the isolated deficiency of xanthine dehydrogenase (XDH), and xanthinuria type II is an autosomal recessive disorder characterized by deficiency of xanthine dehydrogenase and aldehyde oxidase activities due to lack of a common sulfido-molybdenum cofactor (MoCo).

Epidemiology:

The disorder has been reported in one large Bedouin family.

Molecular genetics:

Human Molybdenum Cofactor Sulfurase (HMCS)

A mutation in the C-terminal domain of HMCS identified in a Bedouin-Arab child presenting with urolithiasis the child was homozygous for a c.2326C>T (p.Arg776Cys) mutation,.

References:

Peretz H, Naamati MS, Levartovsky D, Lagziel A, Shani E, Horn I, Shalev H, Landau D. Identification and characterization of the first mutation (Arg776Cys) in the C-terminal domain of the Human Molybdenum Cofactor Sulfurase (HMCS) associated with type II classical xanthinuria. *Mol Genet Metab.* 2007;91:23-29.

Xeroderma pigmentosum

Autosomal recessive (MIM 278700)

Sensitivity to sunlight with the development of carcinoma at an early age is a leading feature of xeroderma pigmentosum. Onset, with freckle-like lesions in exposed areas, usually occurs in the first years of life.

Epidemiology:

The disorder seems to exist in relatively high frequency among Arabs and was diagnosed in several families in Israel.

Molecular genetics:

Gene XPA (chromosomal locus 9q22.3)

A Palestinian patient affected with xeroderma pigmentosum (XP) group A who had severe skin symptoms and neurological abnormalities of the de Sanctis-Cacchione syndrome was homozygous for a nucleotide transition altering the Arg-207 codon (CGA) to a nonsense codon (TGA) [ARG207TER].

References:

Satokata I, Tanaka K, Miura N, Narita M, Mimaki T, Satoh Y, Kondo S, Okada Y
Three nonsense mutations responsible for group A xeroderma pigmentosum. *Mutat Res* 1992;273:193-202.