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MENDELIAN DISORDERS AMONG JEWS

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This catalog is dedicated to the memory of the late Professor Richard M Goodman whose publications and in particular his book on genetic disorders among Jews were the inspiration for this project.

The catalog intends to include the Mendelian disorders that have been reported among Jews and are either relatively frequent, or in which a mutation has been reported with an increased frequency. The catalog includes a very short list of references and mainly refers to McKusick's Mendelian Inheritance in Man.
http:/www.ncbi.nlm.nih.gov/Omim.
The online updated catalog is available at http://server.goldenhelix.org//israeli/

In order to keep the catalog updated and as accurate as possible I need feedback. Please send to me any comment, correction and new data including new mutations zlotogora@gmail.com

Abetalipoproteinemia

Autosomal recessive (MIM 200100)
The first symptoms are early failure to thrive with diarrhea and steatorhea, often with abdominal distention. While with time the steatorhea 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
The disease is relatively frequent among Ashkenazi Jews and was reported in one Iranian Jewish family and one North African (Tunisia/Algeria) family.

Biochemical defect
The absence of the chylomicrons and all lipoprotein particles of the VLDL cascade (all lipoprotein, which contains apolipoprotein B,) is typically found in the affected patients. The cholesterol levels are usually less than half of normal and the triglycerides are markedly reduced and fail to rise after ingestion of fat.

Molecular genetics
Microsomal triglyceride-transfer protein (MTP), gene (chromosomal locus 4q22-24)
The absence of the chylomicrons and all lipoprotein particles of the VLDL cascade
Among Ashkenazi Jews, the mutation p.G865X was found in several patients with a carrier frequency of 1:131. Several patients carried another mutation c.2212delT. In the Iranian Jewish family the parents were consanguineous and the patient was homozygous c.148-2A>G, the patient from Tunisia, Algeria was homozygous p.K03X.

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
Narcisi TM, Shoulders CC, Chester SA, Read J, Brett DJ, Harrison GB, Grantham TT, Fox MF, Povey S, de Bruin TW, et al. Mutations of the microsomal triglyceride-transfer-protein gene in abetalipoproteinemia. Am J Hum Genet 1995 57:1298-1310.

Acute infantile liver failure due to mutations in TRMU gene

Autosomal recessive (MIM 610230)
Acute liver failure in infancy is a life threatng 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.

Epidemiology:
The disease has been reported in seven unrelated Yemenite Jewish families.
In a sample of 120 healthy Yemenite individuals three carriers for Y77H were found (1:40)

Molecular genetics:
TRMU gene (chromosomal locus 22q13)
Five Yemenite Jewish patients were homozygous for Y77H two were heterozygous for this mutation and c.706-1G>A in one and an unknown mutation in the other. One Yemenite Jewish patient was compound heterozygote for c.679C>T (L233F) and c.28G>T (A10S). An Ashkenazi patient was heterozygous for G14S and an unknown mutation.

References
Lev D, Gilad E, Leshinsky-Silver E, Houri S, Levine A, Saada A, Lerman-Sagie T. Reversible fulminant lactic acidosis and liver failure in an infant with hepatic cytochrome-c oxidase deficiency. J Inherit Metab Dis. 2002;25:371-377.
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.

Acyl CoA dehydrogenase deficiency, short/branched chains

Autosomal recessive (MIM 600301)
The clinical phenotype is very heterogeneous, varying from a fatal metabolic decompensation in infancy with metabolic acidosis, failure to thrive, developmental delay, hypotonia and seizures to a more subtle later-onset progressive myopathy or, most commonly, a completely asymptomatic clinical course.
The biochemical phenotype includes urinary excretion of ethylmalonic (EMA) and methylsuccinic (MSA) acids, high C4 acylcarnitine levels and an elevated C4/C2 ratio.

In the newborn screening program in NY five patients of Ashkenazi Jewish descent were found to be homozygous for the 319C>T founder mutation. None have displayed any symptoms of SCADD as yet, despite continuous excretion of EMA and MSA.

Epidemiology:
The disease has been reported in a Georgian and a Moroccan Jewish family as well as 10 Ashkenazi Jewish children.
In a sample of 412 healthy AJ individuals the frequency of carriers for three of the variants, 511C>T, 625G>A and 319C>T, is high (0.058, 0.422 and 0.019, respectively)

Molecular genetics:
ACADSB gene (chromosomal locus 10q25-q26)
The Georgian Jewish patient was homozygous 908G>C and the Moroccan Jewish patient for 443C>T.
The Ashkenazi were either homozygous or heterozygous for c.319C>T

References
Korman SH, Andresen BS, Zeharia A, Gutman A, Boneh A, Pitt JJ. 2-ethylhydracrylic aciduria in short/branched-chain acyl-CoA dehydrogenase deficiency: application to diagnosis and implications for the R-pathway of isoleucine oxidation . Clin Chem. 2005 51:610-617
Pardo S, Kirmse B., Wasserstein M, Scott S., Kornreich R, Desnick RJ , Diaz GA , Edelmann L. A high frequency of acyl-CoA dehydrogenase, short chain (ACADS) variant genotypes among healthy Ashkenazi Jews [abstract 1546]. Presented at the annual meeting of The American Society of Human Genetics, October 26, 2007, San Diego, California.
Tein I, Elpeleg O, Ben-Zeev B, Korman SH, Lossos A, Lev D, Lerman-Sagie T, Leshinsky-Silver E, Vockley J, Berry GT, Lamhonwah AM, Matern D, Roe CR, Gregersen N.Short-chain acyl-CoA dehydrogenase gene mutation (c.319C>T) presents with clinical heterogeneity and is candidate founder mutation in individuals of Ashkenazi Jewish origin. Mol Genet Metab. 2008 93:179-189.

Acyl-CoA dehydrogenase, very long chain deficiency

Autosomal recessive (MIM 201475)
The main clinical features are in infancy: cardiomyopathy, nonketotic hypoglycemia and hepatic dysfunction, skeletal myopathy, or sudden death in infancy with hepatic steatosis. Clinical recognition of VLCAD deficiency is important because it is a treatable cause of cardiomyopathy in children.

Biochemical defect:
VLCAD is loosely bound to the mitochondrial inner membrane and requires detergent for stabilization, while the other 3 acyl-CoA dehydrogenases are readily extractable into the soluble fraction without detergent, indicating that they are located in the mitochondrial matrix. Catalytically, VLCAD has a 10 times higher specific activity toward palmitoyl-CoA than does LCAD. The enzyme was found to catalyze the major part of mitochondrial palmitoyl-CoA dehydrogenation in liver, heart, skeletal muscle, and skin fibroblasts.

Molecular genetics:
VLCAD gene (chromosomal locus 17p11.2-p11.1)
A Jewish patient from Buchara was homozygous for 4bp deletion at nucleotide 799-802 causing a frameshift and termination at position 826. The disease was diagnosed in 2 other families from the same origin (Elpeleg O).
In a Jewish family from Iraq with three siblings presenting with a mild late onset form of the disease -rhabdomyolysis and myoglobunuria- a novel G637A mutation was found in homozygosity.

References:
Watanabe H, Orii KE, FukaoT, SongXQ, Aoyama T, Ijlst L, Ruiter J, Wanders RJ A, Kondo N. Molecular basis of very long chain acyl-CoA dehydrogenase deficiency in three Israeli patients: identification of a complex mutant allele with P65L and K247Q mutations, the former being an exonic mutation causing exon 3 skipping. Hum Mutat 2000 15: 430-438.
Straussberg R, Strauss A. A novel mutation of late-onset very-long-chain acyl-CoA dehydrogenase deficiency. Pediatr Neurol 2002 27:136-137.

Adrenal hyperplasia III (21 OH deficiency)

Autosomal recessive (MIM 201910)
Classical either salt wasting or non salt wasting and non classical. The clinical symptomatology is variable and symptoms may appear at any age.

Epidemiology:
Non classical CAH seems to represent the most frequent autosomal recessive disorder in human, being particularly frequent among Ashkenazi Jews, Hispanics, Italians and Yugoslavs. The prevalence of the disease among the Ashkenazi Jews was calculated to be 1:27 (3.7%). In a sample of 1,000 anonnymous Ashkenazi Jews the carrier frequency of V281L was 17% (5.8% in non-Jewish Europeen control).

Molecular genetics:
CYP21B gene (chromosomal locus 6p21.3)
In a group of 310 Ashkenazi Jewish patients with CAH most were of the non classical type. In this group most cases were either homozygote for the V281L mutation (founder mutation) (65 patients), or compound heterozygotes of this mutation with IVS2 AS-13 (23 patients), a large deletion (21 patients), Q318X (3 patients) or I172N (one patient). Few of the patients with V281L were affected with the classical type of the disease.

References:
Edelmann L, Kornreich RJ, Desnick RJ, Diaz GA. The V281L mutation in the CYP21 gene is a founder mutation that is prevalent among individuals of Ashkenazi and Europeen origin. Am J Hum Genet 2002 71 A1159 370S.
Speiser PW, Dupont B, Rubinstein P, Piazza A, Kastelan A and New MI. High frequency of non-classical steroid 21 ß-hydroxylase deficiency. Am J Hum Genet 1985 37:650-667.
Wilson RC, Nimkarn S, Dumic M, Obeid J, Azar M, Najmabadi H, Saffari F, New MI. Ethnic-specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Mol Genet Metab 2007 90:414-421.

Adrenal hyperplasia IV (11-ß hydroxylase deficiency)

Autosomal recessive (MIM 202010)
The affected children present with symptoms related to androgen and mineralocorticoid excess. At birth, affected females may present with virilization of various degree from mild clitoris enlargement to extreme virilization with external male appearance with empty scrotum, some being reared as males. Later, the androgen excess leads to excessive body growth, advanced epiphyseal maturation, masculine body habitus with increased muscle mass, acne, precocious pubic and axillary hair. Pigmentation of skin and nipples is frequently observed. Many patients have hypertension which may be severe leading to complications; there is no correlation in females between the virilization and the hypertension. In some patients, hypokalemia may be observed.

Epidemiology:
The incidence of the disease among Jews from Morocco was estimated to be 1:5,000 to 1:7,000 with a carrier frequency of 1:35 - 1:42. Many of the families originated from the Atlas Mountains in Morocco and it was speculated that all the affected individuals have a common ancestor who lived in this region.
In another survey of 236 random healthy individuals from Morocco the carrier frequency was found to be 1:118

Biochemical defect:
The diagnosis is based on the finding of elevated urinary excretion of tetrahydro-11-deoxycortisol and or plasma 11-deoxycortisol levels.

Molecular genetics:
CYP11B1 gene (chromosomal locus 8q22)
The 11 ß-hydroxylase gene CYP11B1 is located on chromosome 8q22 together with the highly homologous gene CYP11B2 which may be a pseudogene or alternatively a gene whose product may be required for aldosterone synthesis. The major mutation among Jewish patients originating from Morocco is R448H another mutation that was found in one patient was R448C.
One Iranian Jewish patient was homozygous for InsGTG464

References:
Paperna T, Gershoni-Baruch R, Badarneh K, Kasinetz L, Hochberg Z. Mutations in CYP11B1 and Congenital Adrenal Hyperplasia in Moroccan Jews. J Clin Endocrinol Metab. 2005 90:5463-5465.
Rösler A, Lieberman E and Cohen T. High frequency of congenital adrenal hyperplasia (11 ß hydroxylase deficiency) among Jews from Morocco. Am J Med Genet 1992 42:827-834.
White PC, Dupont J, New MI, Leiberman, Hochberg Z, Rösler A. A mutation in CYP11B1 (Arg -448 -- His) associated with steroid 11 ß-hydroxylase deficiency in Jews of Moroccan origin. J Clin Invest 1991 87:1664-1667.

Adrencorticotropic hormone deficiency (ACTH deficiency)

Autosomal recessive (MIM 201400)
Isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) is a rare cause of adrenocortical insufficiency, especially in children, and may be an underestimated cause of neonatal death. Early postnatal diagnosis may prevent hypoglycemic seizures, Addisonian crises, and death.

Epidemiology:
The disease was reported in a family of Jews from India that were first cousins

Molecular genetics:
T box 19 gene (chromosomal locus 1q23-q242)
The patient was homozygous for IVS4+1G>A

References:
Weintrob N, Drouin J, Vallette-Kasic S, Taub E, Marom D, Lebenthal Y, Klinger G, Bron-Harlev E, Shohat M.Low estriol levels in the maternal triple-marker screen as a predictor of isolated adrenocorticotropic hormone deficiency caused by a new mutation in the TPIT gene. Pediatrics. 2006 e322-327.

Adrenoleukodystrophy

X linked (MIM 300100)
X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder characterized by impaired peroxisomal betaoxidation of very-long-chain fatty acids (VLCFAs). This is probably due to reduced activation of the VLCFAs and results in demyelination of the nervous system and adrenocortical insufficiency.

Epidemiology and molecular genetics:
ALD gene (gene location Xq28)
The disorder was reported in three different families from Morocco with a same mutation [L229P] suggesting a founder effect. The other Jewish families studied had each a different mutation. In blood samples of 7 Jewish (5 Sephardi and 2 Ashkenazi) and 3 Arab Israeli families suffering from ALD several mutations were identified: R104H, Y174C, R401Q, G512C, R464X, Y171 and E471.

References:
Neumann S, Topper A, Mandel H, Shapira I, Golan I, Gazit E, Loewenthal R. Identification of new mutations in Israeli patients with X linked adrenoleukodystrophy. Genetic Testing 2001 5:65-68.

Afibrinogenemia congenital

Autosomal recessive (MIM 607039)
Two unrelated large sibships, including 10 cases of congenital afibrinogenemia among 27 sibs, are reported. Both sibships were the product of uncle-niece marriages. They were not selected for any particular clinical manifestation and should provide some information on genetic fitness. Six of the patients died in childhood, two affected boys are adolescent and two affected patients are young women. Two of the four survivors had spontaneous ruptures of the spleen.

Epidemiology
The disorder was described in an Iraqi Jewish sibship and in a Moroccan Jewish kindred.

Molecular genetics
The phenotype is the result of mutations in one or another of the 3 fibrinogen genes, alpha (FGA), beta (FGB), or gamma (FGG).

References
Fried K, Kaufman S. Congenital afibrinogenemia in 10 offspring of uncle-niece marriages. Clin Genet 1980 17: 223-227.

AGAT deficiency

Autosomal recessive (MIM 612718)
The presentation is characterized by nonspecificpsychomotor, especially language developmental delay. In the Yemenite Jewish patients failure to thrive was particularly impressive and muscle involvement manifesting as proximal muscle weakness, fatigability and myopathic EMG.

Epidemiology and Molecular genetics
GAMT gene (chromosomal location 15q15.3)
The disorder was described in a Yemenite Jewish sibship, the patients were homozygote for the mutation 1111_1112 insA producing a frameshift at Met371 and a premature termination at codon 376.the mutation was not found in a sample of 57 anonymous Yemenite Jews.

References
Edvardson S, Korman SH, Livne A, ShaagA, Saada A, Nalbandian R, Allouche-Arnon H, Gomori J M, Katz-Brull R. L-arginine:glycine amidinotransferase (AGAT) deficiency: clinical presentation and response to treatment in two patients with a novel mutation. Molecular Genetics and Metabolism 2010 101:228-232.

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 and molecular genetics
SAMHD1 gene (chromosomal locus 20q11)
Four mutations were identifies in several Ashkenazi Jewish families. The most frequent mutation was a deletion in exon 1(8 out 1109 control 0.751%). Other mutations were: c.676C>G (0.087%) and c.649_650insG (0.097%). The mutation c.1106T>C was found in a single allele.

References
Jalas et al. Aicardi Goutieres syndrome carrier screening in Ashkenazi Jewish families ASHG 2013
Leshinsky-Silver E, Mlinger G, Ben Sira L, Kidron D, Cohen S, Inbar S, Bezaleli T, Levine A,Vinkler C, Lev D, Lerman-Sagie.A large homozygous deletion in the SAMHD1 gene causes atypical Aicardi-Goutieres syndrome associated with mtDNA deletions. Eur J Hum Genet 2011 19:287-292.

Albinism oculocutaneous

Autosomal recessive (MIM 203100)

Epidemiology:
The disorder is relatively more frequent among Jews from Morocco with an estimated incidence of 1:10,000.

Molecular genetics
Tyrosinase gene (gene location 11q14-q21)
The predominant allele causing albinism among Moroccan Jews is G47D (1.7% allele frequency). The same mutation was also found to be frequent in patients from Puerto Rico. The same mutation was also found with the same RFLP haplotype among patients from the Canary Island Puerto Rico and the United States. The most probable explanation of the dispersion of the mutation may be a common origin that may be linked to the expulsion of Jews from Spain and their dispersion (Morocco, Portugal or Canary Islands either remaining Jews or converted to Christianity). This hypothesis is supported by the absence of the mutation in other Jewish communities form the Mediterranean region.

References:
Gershoni-Baruch R, Rosenmann A, Droetto S, Holmes S, Tripathi RK, Spritz RA. Mutations of the tyrosinase gene among patients with oculocutaneous albinism from various ethnic groups in Israel. Am J Hum Genet 1994 54:586-594.

Alport syndrome

X-linked inheritance (MIM 301050)
Autosomal recessive (MIM 203780)
The predominant clinical features are nephritis and hearing loss. The carriers are often symptomatic.

Molecular genetics:
COL4A5 gene (gene location X q22.3)
Mutations in the basement membrane collagen gene COL4A5 cause Alport syndrome. The mutation R1677Q was found in several non related families of Ashkenazi Jewish
COL4A3 gene (gene location 2q35-37)
The mutation c.40_63del was found in homozygosity in a family of Ashkenazi Jewish origin.Six among 1017 Ashenazi individuals were carriers of the mutation (1:183), the mutation was found in other populations.

References:
Barker DF, Denison JC, Atkin CL, Gregory MC. Common ancestry of three Ashkenazi American families with Alport syndrome and COL4A5 R1677Q. Hum Genet 1997 99:681-684.
Webb BD, Brandt T, Liu L, Jalas C, Liao J, Fedick A, Linderman MD, Diaz GA, Kornreich R, Trachtman H, Mehta L, Edelmann L. A founder mutation in COL4A3 causes autosomal recessive Alport syndrome in the Ashkenazi Jewish population. Clin Genet. 2014;86:155-160.

Argininemia

Autosomal recessice inheritance (MIM 207800)
Arginase deficiency is an autosomal recessive inborn error of metabolism caused by a defect in the final step in the urea cycle, the hydrolysis of arginine to urea and ornithine.The disorder is characterized as the other urea cycle disorders by the triad of hyperammonemia, encephalopathy, and respiratory alkalosis

Epidemiology and Molecular genetics:
Arginase gene (gene location 6 q23)
An exon 2 deletion was reported in an Ashkenazi patient from Ashkenazi origin. Another mutation D128G was reported in several other patients of Ashenazi origin. These mutations were not found in 760 Ashkenazi Jewish DNA samples.

References:
Staretz-Chacham, Goldstein N, Ben-Zeev B, Loewenthal R, Mandel H, Sigalov E, Vielenski B, CohenY, CEderbaum SD, Aniskter Y. A novel deletion mutation in ARG1 gene found in a neonate ASHG abstract 1519 2007

Arthrogryposis, autism spectrum disorder and epilepsy

Autosomal recessive

The syndrome was reported in 8 patients from three related families of Ashkenazi Jewish origin.

At birth knee and hip dislocation and contracture of the fingers were diagnosed. The contractures did not changed with time. Other findings were micrognathia and muscle hypotonia. All the children had retarded psychomotor development, seizure disorder and presented with symptoms compatible with autism spectrum. Mild to moderate mental retardation was present in all the children.

Seizures were noted at 3-11 years of age and first as localization related or atypical absence and controlled by antiepileptic drugs.

Molecular genetics:

SLC35A3 gene (chromosomal location)

All the patients were compound heterozygous for c.514C>T and 886A>G.

Among 2045 anonymous Ashkenazi Jews 10 were carriers of 886A>G (1:205)

References:

Edvardson S, Ashikov A, Jalas C, Sturiale L, Shaag A, Fedick A, Treff NR, Garozzo D, Gerardy-Schahn R, Elpeleg O.Mutations in SLC35A3 cause autism spectrum disorder, epilepsy and arthrogryposis. J Med Genet. 2013;50:733-739.

Ataxia telangiectasia

Autosomal recessive (MIM 208900)
The predominant clinical features are neurological symptoms manifested in walking difficulties. The cerebral dysfunction is first manifested as ataxia and later by choreoathetosis, myoclonic jerking and occulomotor 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, such as cafe au lait spots, vitiligo and loss of subcutaneous fat may also be present. Hormonal dysfunction is common and can be manifested by delayed or even absent secondary sexual development in females. Variable immunodeficiency is also found in patients affected with ataxia telangiectasia, which may lead to recurrent upper respiratory and lung diseases. The patients have increased risk for cancer and more than 15% die from malignant diseases. Lymphomas are common in childhood while adult patients have increased incidence of gastric carcinoma, and T cell lymphatic leukemia. The predominant cause of death is infections. Most patients have normal intelligence.
There are some indications that heterozygotes may have an increased risk to develop cancer when compared to the general population. However no definite conclusion has been drawn so far.
The diagnosis is based on cytogenetic examination, in which a high frequency of spontaneous chromosome aberrations, mainly breaks, is demonstrated. Chromosomes 14q and 7 are predominantly involved in breaks and translocations.

Epidemiology:
Ataxia telangiectasia is found with an increased frequency among Jews from Morocco and Tunisia. Its estimated incidence is to be 1:26500, with a carrier frequency of of 1/80 in the screening for the mutation in a random sample.

Biochemical defect:
Ataxia telangiectasia is one of the chromosome instability syndromes. There is high in-vitro sensitivity to ionizing radiations and radiomimetic chemicals such as bleomycin and neocarcinostatin.

Molecular genetics:
ATM gene (gene location 11q22-23)
A single mutation 103C→T resulting in a stop codon at position 35 of the ATM protein was found in 32 out of 33 alleles in Jewish families from North Africa.
In two families of Yemenite origin (in each case the parents were consanguineous) the child was homozygous for delA368, the mutation frequency has not yet been investigated (M Frydman)

References:
Gilad S, Bar-Shira A, Harnick R, Shkedy D, Ziv Y, Khosravi R, Brown K et al.. Ataxia telangiectasia: founder effect among North African Jews. Human Mol Genet 1996 5:2033-2037.
Levin S, Gottfried E and Cohen M. Ataxia telangiectasia: A review with observations on 47 Israeli cases. Pediatrics 1977 6:135.

Asparagine synthetase deficiency

Autosomal recessive (MIM 615574)
ASNS deficiency is a severe neurologic disorder characterized by microcephaly, severely delayed psychomotor development, progressive encephalopathy, cortical atrophy, and seizure or hyperekplexic activity. The disorder shows onset in utero or at birth and may result in early death
Some of the patients develop early-onset seizures, including tonic, myoclonic, generalized tonic-clonic, and partial complex seizures associated with multiple independent spike foci or suppression burst patterns on EEG. In one family the affected children had hypsarrhythmia and in another one they did not have overt seizures, but showed hyperekplexia and jitteriness with disorganized background activity on EEG. Brain imaging showed decreased cerebral volume with enlarged lateral ventricles. Some patients had cerebellar hypoplasia, pontine hypoplasia, thin corpus callosum, simplified gyral pattern, cortical dysgenesis, and/or delayed myelination. Other more variable features included dysmorphism, such as micrognathia, receding forehead, and large ears, axial hypotonia, and cortical blindness. Most had feeding difficulties and respiratory insufficiency, and several patients died in infancy.

Epidemiology and molecular Genetics:
Asparagine syntetase (chromosomal locus 7q21.3)
A mutation p.F361V (c.1084T>G) was found in homozygozity in two Jewish Iranian families

References:
Ruzzo EK, Capo-Chichi JM, Ben-Zeev B, Chitayat D, Mao H, Pappas AL, Hitomi Y, Lu YF, Yao X, Hamdan FF, Pelak K, Reznik-Wolf H, Bar-Joseph I, Oz-Levi D, Lev D, Lerman-Sagie T, Leshinsky-Silver E, Anikster Y, Ben-Asher E, Olender T, Colleaux L, Décarie JC, Blaser S, Banwell B, Joshi RB, He XP, Patry L, Silver RJ, Dobrzeniecka S, Islam MS, Hasnat A, Samuels ME, Aryal DK, Rodriguiz RM, Jiang YH, Wetsel WC, McNamara JO, Rouleau GA, Silver DL, Lancet D, Pras E, Mitchell GA, Michaud JL, Goldstein DB. Deficiency of asparagine synthetase causes congenital microcephaly and a progressive form of encephalopathy. Neuron. 201316;80:429-441.

Atrichia, congenital

Autosomal recessive (MIM 203655, 209500)
Inherited universal alopecia without ectodermal defects is very rare. Patients are born with normal hair but this is shed almost completely during the first weeks or months of life and never regrows. In many families the development of papular lesions is noted as an additional phenotypic feature, which defines a related phenotype designated as atrichia with papular lesions. In this form of the disease a diffuse papular rash over the entire skin surface is often present in a later stage.

Epidemiology and molecular Genetics:
Hairless gene, HR (chromosomal locus 8p21.2)
A mutation c.1557-1G>T was found in homozygozity in a consanguineous Jewish Iranian child with congenital atrichia and in compound heterozygosity in the paternal side of another patient with congenital atrichia (Iraqi Jewish orign). On the maternal side of the patient (Moroccan Jewish origin) another mutation Q478X was characterized.
In one consanguineous Jewish family of Libyan origin with atrichia with papular lesions the patient was homozygous for a frameshift 11 base pair deletion in exon2.

References:
Betz RC, Indelman M, Pforr J, Schreiner F, Bauer R, Bergman R, Lentze MJ, Nothen MM, Cichon S, Sprecher E. Identification of mutations in the human hairless gene in two new families with congenital atrichia. Arch Dermatol Res. 2007 299:157-161.
Paller AS, Varigos G, Metzker A, Bauer RC, Opie J, Martinez-Mir A, Christiano AM, Zlotogorski A. Compound heterozygous mutations in the hairless gene in atrichia with papular lesions. J Invest Dermatol. 2003 121:430-422.
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.

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) Polyglandular deficiency syndrome

Autosomal recessive (MIM 240300)
Polyglandular deficiency syndrome is characterized by hypoparathyroidism (HPT), adrenal insufficiency and chronic mucocutaneous candidiasis, but none of its components is constant. Occasionally, symptoms of other immune disorders, like pernicious anemia, alopecia or gonadal failure are present. Most cases present with HPT since it occurs early before the second decade, and may remain the only manifestation of the syndrome. It is to note that while candidiasis is usually found in almost 100% of the affected patients, it was rarely observed among the Iranian Jewish patients. The syndrome is variable as for the age of onset, the type of manifestation and the severity of the symptoms, the variability is also intrafamilial.

Epidemiology:
The incidence of the disease was calculated to be 1:10,000 in the Iranian Jewish community.

Molecular genetics:
AIRE gene (chromosomal locus 21q22.3)
All the Iranian Jewish patients examined have a unique mutation [Y85C] with a founder haplotype.

References:
Bjorses P, Aaltonen J, Vikman A, Perheentupa J, Ben-Zion G, Chimuello G, Dahl N, Heideman P. Hoorweg-Nijman JJG., Mathivon L, Mullis PE, Pohl M, Rizen M, Romeo G, Shapiro MS, Smith CS, Solyom J, Zlotogora J, Peltonen L. Genetic homogeneity of autoimmune polyglandular syndrome type I. Am J Hum Genet 1996 59:879-886.
Bjorses P,Halonen M, Palvimo JJ, Kolmer M, Aaltonen J, Ellonen P, Perheentupa J, Ulmanen I, Peltonen L. Mutations in the AIRE gene. Effects on subcellular location and transactivation function of the autoimmune polyendocrinopathy candidiasis ectodermal dystrophy protein. Am J Hum Genet 2000 66 378-392.
Zlotogora J, Shapiro MS. Polyglandular autoimmune syndrome in Iranian Jews. J Med Genet 1992 29:834-836.

Autoinflamation, lipodystrophy and dermatosis syndrome (ALDD) CANDLE syndrome

Autosomal recessive (MIM 256040)
Most patients present within the first 2-4 weeks of life with fever and repeated attacks of erythematous and violaceous, annular cutaneous plaques, lasting for a few days or weeks and leaving residual purpura. Later during infancy, patients develop persistent periorbital erythema and edema, finger or toe swelling and hepatomegaly with variable elevation of acute phase reactants. Other common clinical features that developed in the first years of life included progressive loss of peripheral fat (lipodystrophy), failure to thrive, lymphadenopathy and hypochromic or normocytic anemia.

Epidemiology and molecular genetics:
PSMB8 gene (chromosomal locus 6p21)
The disease has been reported in an Ashkenazi patient homozygous for c.405C>A (p.CC135X).

References:
Liu Y, Ramot Y, Torrelo A, Paller AS, Si N, Babay S, Kim PW, Sheikh A, Lee CC, Chen Y, Vera A, Zhang X, Goldbach-Mansky R, Zlotogorski A. Mutations in PSMB8 cause CANDLE syndrome with evidence of genetic and phenotypic heterogeneity. Arthritis Rheum. 2012;64:895-907.

Autosomal dominant partial epilepsy with auditory features (ADPEAF)

Autosomal dominant (MIM 600512)

Epidemiology:
The disease was reported in two Ashkenazi Jewish families

Molecular genetics:
LGI1 gene (chromosomal location 10q24)
In one family the mutation [G42G] was found

References:
Berkovic SF, Izzillo P, McMahon JM, Harkin LA, McIntosh AM, Phillips HA, Briellmann RS, Wallace RH, Mazarib A, Neufeld MY, Korczyn AD, Scheffer IE, Mulley JC. LGI1 mutations in temporal lobe epilepsies. Neurology. 2004 13;62:1115-1119

Bardet-Biedl 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 and molecular genetics:
BBS2 gene (chromosomal locus 16q21)
Four patients from three families were diagnosed among ultraorthodox Jews two were homozygous affected for the c.311A>C (rs121908179) mutation and two were compound heterozygous for this mutation along with the c.1895G>C mutation.
The population carrier frequency was 0.473% (±0.0071%) for the c.311A>C mutation and 0.261% (±0.0064%) for the c.1895G>C mutation.
Shevach et al reported four Ashkenazi families with individuals affected with non syndromic retinitis pigmentosa in which the patietns were homozygous or compound heterozygous for these two mutations.

References:
Fedick A, Jalas C, Abeliovich D, Krakinovsky Y, Ekstein J, Ekstein A, Treff N. Carrier frequency of two BBS2 mutations in the Ashkenazi population. Clin Genet. 2014;85:578-582
Shevach E, Ali M, Mizrahi-Meissonnier L, McKibbin M, El-Asrag M, Watson CM,; Inglehearn CF, Ben-Yosef T, Blumenfeld A, Jalas C, Banin E, Sharon D. Association Between Missense Mutations in the BBS2 Gene and Nonsyndromic Retinitis Pigmentosa. JAMA Ophthalmology Published online December 26

Best disease

Autosomal (MIM 153700)
Best Vitelliform macular dystrophy, is a progressive macular degeneration. Early on, the fundus usually appears normal; a typical "egg-yolk" macular lesion may subsequently develop, and disruption of this lesion follows, usually accompanied by a drop in visual acuity and culminating in macular atrophy.
RPE function as measured by electro-oculography is markedly affected from very early on. Progression of the disease leads to destruction of the RPE and overlying photoreceptors in the macular area, often culminating in loss of central vision in late adolescence or adulthood.
Best disease shows an autosomal dominant inheritance in the majority of cases.

Molecular genetics:
BEST1 gene (gene location 11q13))
The disease has been reported in one Ashkenazi Jewish family in which it was inherited as an autosomal recessive trait due to an homozygous mutation c.1415delT, pLeu472ProfX10

References:
Bitner H, Mizrahi-Meissonnier L, Griefner G, Erdinest I, Sharon D, Banin E. A homozygous frameshift mutation in BEST1 causes the classical form of Best disease in an autosomal recessive mode. Invest Ophthalmol Vis Sci 2011;52:5332-5338

Bloom syndrome

Autosomal recessive (MIM 210900)
The most prominent clinical symptom is the severe pre and post natal growth retardation. The majority of Bloom syndrome patients are shorter than 160 cm with normal body proportions and occasionally slight microcephaly. Other clinical features include sun sensitive facial lesions and male infertility due to lack of spermatogenesis. There is an unusually high rate of neoplasia so that most patients develop various types of cancer usually in the second decade of life, including leukemia, lymphoma, Hodgkin disease and various carcinomas.
The cytogenetic diagnosis of Bloom syndrome is the demonstration of increased spontaneous sister chromatid exchanges (SCE).

Epidemiology:
The incidence among the Ashkenazi Jews was calculated to be 1:60,000 to 1:100,000. In a summary of 10,009 controls 85 (1/118) were found to be carriers. In one study a twofold increased lifetime risk for colorectal cancer was found for carriers of Bloom syndrome among Ashkenazi Jews but was not confirmed in another study.
The mutation had been segregating in the Ashkenazi Jews for 35 (20-54) generations. It is interesting to note that the same mutation was also found in several non-Jewish patients of Spanish origin probably because of a common founder.
The syndrome has been reported in one Iranian Jewish patient

Molecular genetics:
BLM gene (gene location 15q26.1)
Among 63 chromosomes found among Bloom syndrome Ashkenazi Jewish patients 61 had the same 6bp deletion/7bp insertion at the nucleotide 2281 cDNA of the BLM gene (97%) and 2 had another mutation (c.2407-2408dupT). Two Jewish patients were compound heterozygous for the Ashkenazi Jewish founder mutation and another private mutation: c.98+1G>T (Sepahradi) and c.3510T (unknown origin)

References:
Cleary SP, Zhang W, Di Nicola N, Aronson M, Aube J, Steinman A, Haddad R, Redston M, Gallinger S, Narod SA, Gryfe R Heterozygosity for the BLM (Ash) mutation and cancer risk. Cancer Res. 2003 63:1769-1771.
Ellis NA, Ciocci S, Proytcheva M, Lennon D, Groden J, German J. The Ashkenazic Jewish Bloom syndrome mutation blmAsh is present in non-Jewish Americans of Spanish ancestry. Am J Hum Genet 1998 63:1685-93.
German J.; Bloom D.; Passarge E.; Fried K, Goodman R. M, Katzenellenbogen I, German J, Sanz MM, Ciocci S, Ye TZ, Ellis NA. Syndrome-causing mutations of the BLM gene in persons in the Bloom's syndrome registry. Hum Mutat. 2007 Aug;28:743-753
Laron Z, Legum C, Levine S, Wahrman J. Bloom's syndrome. VI. The disorder in Israel and an estimation of the gene frequency in the Ashkenazim. Am. J. Hum. Genet. 1977 29:553-562.
Legum C, Furman V, Diamant S. Bloom's syndrome in an Iranian Jewish male. Ann Genet 1991 34:198-200.
Peleg L, Pesso R, Goldman B, Dotan K, Omer M, Friedman E, Berkenstadt M, Reznik-Wolf H, Barkai G. Bloom syndrome and Fanconi's anemia: rate and ethnic origin of mutation carriers in Israel. Isr Med Assoc J 2002 4:95-97.

Breast and ovarian cancer, predisposition

Autosomal dominant (MIM 113705, 600185)
Several mutations in BRCA1 and BRCA2 genes, responsible for breast and ovarian cancer are relatively frequent among Jews.

Epidemiology and molecular genetics:
Based on population screening among Ashkenazi Jews the carrier frequency of the mutations in BRCA1 was estimated to be 0.9% for 185delAG and 0.13% for 5382insC. The carrier frequency of the mutation 6174delT in BRCA2 was estimated to be 0.9-1.5%.
The 185delAG mutation in BRCA1 was also found among Iraqi and Moroccan Jews at rates comparable to Ashkenazi Jews.
Another mutation 8765 delAG in BRCA2 was found to be relatively frequent among Jews from Yemen.
In patients of Sephardic origin 2 founder mutations were reported: p.A1708E in BRCA1 and c.67 + 1G > A (IVS2 + 1G > A) in BRCA2.

References:
Bar-Sade RB, Kruglikova A, Modan B, Gak E, Hirsh-Yechezkel G, Theodor L, Novikov I, Gershoni-Baruch R, Risel S, Papa MZ, Ben-Baruch G, Friedman E.
The 185delAG BRCA1 mutation originated before the dispersion of Jews in the diaspora and is not limited to Ashkenazim. Hum Mol Genet 1998;7:801-805.
Lerer I, Wang T, Peretz T, Sagi M, Kaduri L, Orr-Urtreger A, Stadler J, Gutman H, Abeliovich D The 8765delAG mutation in BRCA2 is common among Jews of Yemenite extraction. Am J Hum Genet 1998 63:272-274.
Oddoux C, Struewing JP, Clayton CM, Neuhausen S, Brody LC, Kaback M, Haas B et al. The carrier frequency of the 6174delT BRCA2 mutation in Ashkenazi Jewish individuals is approximately 1%. Nature Genet 1996;14:188-190.
Sagi M, Eilat A, Ben Avi L, Goldberg Y, Bercovich D, Hamburger T, Peretz T, Lerer I. Two BRCA1/2 founder mutations in Jews of Sephardic origin. Fam Cancer. 2011 10:59-63.
Struewing JP, Abeliovich D, Peretz T, Avishai N, Kaback MM, Collins FS, Brody LC. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nature Genet 1995;11:198-200.

Brittle cornea syndrome

Autosomal recessive (MIM 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. It was noted that all the Jewish patients of Tunisian origin have also red hair as an unusual finding in the family; in one affected child from this ethnic group the hair was of normal color.
The diagnosis is based on the clinical picture only.

Molecular genetics and epidemiology:
ZNF469 (Chromosomal locus 6q24)
The disease was reported with an increased frequency among Tunisian Jews; it seems that the relatively high incidence in this small ethnic group is due to a founder effect.
All the Tunisian Jewish patients are homozygous for a 1bp deletion [5943 delA]. The gene is linked to the hair color gene MCR1, linkage desiquilibrium explaining the red hair in the Jewish Tunisian patients. In 200 random chromosomes from Tunisian Jews the mutation was not detected

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. Epub 2008 May 1.
Abu A, Frydman M, Marek D, Pras E, Stolovitch C, Aviram-Goldring A, Rienstein S, Reznik-Wolf H, Pras E.Mapping of a gene causing brittle cornea syndrome in tunisian jews to 16q24. Invest Ophthalmol Vis Sci. 2006;47:5283-5287.
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.

Brugada syndrome

Autosomal dominant (MIM 601144)
Idiopathic ventricular fibrillation in patients with an electrocardiogram (ECG) pattern of right bundle branch block and ST-segment elevation in leads V1 to V3 is associated with a high incidence of syncopal episodes or sudden death.

Epidemiology:
The syndrome was reported in 3 Ashkenazi Jewish and Moroccan Jewish families.

Molecular genetics:
SCN5A (chromosomal locus)
In one of the families Moroccan origin G35S was identified and R104Q in another family of Moroccan origin

References
Levy-Nissenbaum E, Eldar M, Wang Q, Lahat H, Belhassen B, Ries L, Friedman E, Pras E. Genetic analysis of Brugada syndrome in Israel: two novel mutations and possible genetic heterogeneity.Genet Test 2001;5:331-334.

Calcinosis, tumoral normophosphatemic.

Autosomal recessive (MIM 610455)
Abnormal deposition of calcium salts within skin tissues is known as calcinosis cutis. Inherited calcinosis cutis is known as familial tumoral calcinosis. Two forms of familial tumoral calcinosis havebeen reported in the literature, hyperphosphatemic familial tumoral calcinosis is caused by increased renal reabsorption of phosphate and result in elevated circulating phosphate and formation of periarticular sub-cutaneous calcified masses sometimes associated with bone and tooth defects. In contrast, calcified tumor formation in normophosphatemic familial tumoral calcinosis is generally preceded by a vasculitis-like rash and is associated with inflammatory manifestations mostly evident in mucosal tissues.
Normophosphatemic familial tumoral calcinosis (NFTC) is an autosomal recessive disorder characterized bycalcium deposition in skin and mucosae and associated with unremitting pain and life-threatening skin infections.

Epidemiology:
The disease has been reported in several Jewish patients of Yemenite origin. The carrier frequency among Yemenite Jews is 1:25 (sample of 154 individuals), 1:31 for [K149E] and 1:154 for [R344X].

Molecular genetics:
SAMD9 (chromosomal locus 7q21-7q21.3)
The major mutation is [K149E], another mutation [R344X] was found in compound heterozygosity in one family.

References:
Chefetz I, Amitai DB, Browning S, Skorecki K, Adir N, Thomas MG, Kogleck L, Topaz O, Indelman M, Uitto J, Richard G, Bradman N, Sprecher E. Normophosphatemic Familial Tumoral Calcinosis Is Caused by Deleterious Mutations in SAMD9, Encoding a TNF-alpha Responsive Protein J Invest Dermatol. 2008;128:1423-1429.
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, Indelman M, Chefetz I, Geiger D, Metzker A, Altschuler Y, Choder M, Bercovich D, Uitto J, Bergman R, Richard G, Sprecher E.A deleterious mutation in SAMD9 causes normophosphatemic familial tumoral calcinosis.Am J Hum Genet. 2006;79:759-764.

Camurati-Engelmann disease

Autosomal dominant (MIM 131300)
Camurati-Engelmann disease, progressive diaphyseal dysplasia, or diaphyseal dysplasia Camurati-Engelmann is a rare, autosomal dominantly inherited bone disease, characterised by progressive cortical expansion and sclerosis mainly affecting the diaphyses of the long bones associated with cranial hyperostosis. The main clinical features are severe pain in the legs, muscular weakness, and a waddling gait.

Epidemiology:
The disease has been reported in a large Iraqi-Jewish family.

Biochemical defect:
Deficiency of the enzyme aspartoacylase which may be demonstrated in cultured fibroblasts. There is an increased concentration of N-acetylaspartic acid in plasma and excessive excretion in urine of the patients.

Molecular genetics:
Transformaing growth factor β1gene TGFβ1 (chromosomal locus 19q13*3)*

References:
Janssens K, Gershoni-Baruch R, Guanabens N, Migone N, Ralston S, Bonduelle M, Lissens W, Van Maldergem L, Vanhoenacker F, Verbruggen L, Van Hul W. Mutations in the gene encoding the latency-associated peptide of TGF-beta 1 cause Camurati-Engelmann disease.Nat Genet. 2000;26:273-275.
Janssens K, Gershoni-Baruch R, Van Hul E, Brik R, Guanabens N, Migone N, Verbruggen LA, Ralston SH, Bonduelle M, Van Maldergem L, Vanhoenacker F, Van Hul W. Localisation of the gene causing diaphyseal dysplasia Camurati-Engelmann to chromosome 19q13. J Med Genet 2000;37:245-249.

Canavan disease

Autosomal recessive (MIM 271900)
Canavan disease is a rare degenerative disease of the brain in which the first symptoms appear very early in life. In most cases, the child does not control his head or does not follow at the age of 2-3 months. The first symptoms may also be the appearance of seizures, the presence of hypotonia or a bizarre cry. There is a definite impairment of motor function and the tone changes to spasticity around the age of 6 months. Abnormal postures of hands and feet, as well as increased reflexes, clonus and a positive Babinski sign may be noted at this stage. Usually, the children develop strabismus by the age of 8 months and the progressive eye involvement results in optic atrophy and blindness with roving movements of the eyes and nystagmus. Progressive enlargement of the head is a common feature of the disease.

Epidemiology:
The disease has been reported with an increased frequency among Ashkenazi Jews. Most of the Ashkenazi Jewish patients originated from Eastern Europe. The carrier rate among the Ashkenazi Jews was estimated to be 1:59 by mutation analysis.

Biochemical defect:
Deficiency of the enzyme aspartoacylase which may be demonstrated in cultured fibroblasts. There is an increased concentration of N-acetylaspartic acid in plasma and excessive excretion in urine of the patients.

Molecular genetics:
Aspartoacylase gene ASPA (chromosomal locus 17pter-p13)
One major mutation is found among the Ashkenazi Jews [E285A] that accounted for 83% of the alleles in the US and all the alleles of the Israeli patients. The second mutation found to be frequent in the US is [Y231X] that was found in 15% of the alleles.

References:
Elpeleg ON, Anikser Y, Barash V, Branski D, Shaag A. The frequency of the C854 mutation in the aspartoacylase gene in Ashkenazi Jews in Israel. Am J Hum Genet 1994;55:287-288.
Kaul R, Gao P, Aloya M, Balamurugan K, Petrosky A, Michals K, Matalon R. Canavan disease; mutations among Jewish and non-Jewish patients. Am J Hum Genet 1994;55:34-41.
Ungar M, Goodman RM. Spongy degeneration of the brain in Israel: a retrospective study. Clin Genet 1983;23:23-29.

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. In 2 Ashkenazi Jewish sibs with the antenatal form of CPT II deficiency periventricular calcifications and markedly enlarged kidneys were identified in the fifth gestational month.
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. The disease seems relatively frequent among Ashkenazi Jews, presenting mostly with the adult form of CPT II deficiency.

Epidemiology:
No study on the frequency of the disorder of the mutations have been reported

Molecular genetics:
Carnitine palmitoyltransferase II gene CPTII (chromosomal locus 1p32)
Two mutations on a same allele were found in Ashkenazi patients: one in exon 4 of the CPT2 gene [1237delAG] and a missense mutation [F448 L]. In addition adult Ashkenazi Jewish patients are compound heterozygotes for this mutation and [S113L].

References:
Elpeleg, ON, Hammerman C, Saada A, Shaag A, Golzand E, Hochner-Celnikier D, Berger I, Nadjari M. Antenatal presentation of carnitine palmitoyltransferase II deficiency. Am J Med Genet 2001;102:183-187.
Taggart RT, Smail D, Apolito C, Vladutiu GD. Novel mutations associated with carnitine palmitoyltransferase II deficiency. Hum Mutat. 1999;13:210-220.

Cataracts, autosomal recessive

Molecular genetics:

- *CRYAA gene (chromosomal locus 21q223)* **(MIM 123580)**

Autosomal recessive A homozygous nonsense mutation [W9X] was reported in inbred Jewish family from Iran.

- *LIM2 gene (chromosomal locus 19q134)* **(MIM 154045)**

Autosomal recessive In an inbred Iraqi Jewish family with presenile cataract first noticed between the ages of 20 and 51 years a homozygous T-->G change resulting in a phenylalanine-to-valine substitution at position 105 of the protein was characterized.

- Autosomal dominant (chromosomal locus 14q22-23). In a Moroccan Jewish family with posterior polar cataract the locus was mapped to 14q

References:

Pras E, Levy-Nissenbaum E, Bakhan T, Lahat H, Assia E, Geffen-Carmi N, Frydman M, Goldman B, Pras E.A nonsense mutation (W9X) in CRYAA causes autosomal recessive cataract in an inbred Jewish Persian family. Invest Ophthalmol Vis Sci 2000; 41:3511-3515.

Pras E, Frydman M, Levy-Nissenbaum E, Bakhan T, Raz J, Assia EI, Goldman B, Pras E.A missense mutation in the LIM2 gene is associated with autosomal recessive presenile cataract in an inbred Iraqi Jewish family. Am J Hum Genet 2002;70:1363-1367.

Pras E, Mahler O, Kumar V, Frydman M, Gefen N, Pras E, Hejtmancik JF.A new locus for autosomal dominant posterior polar cataract in Moroccan Jews maps to chromosome 14q22-23. J Med Genet. 2006;43:e50.

Cerebral Cavernous Malformations

Autosomal dominant (MIM 116860)
Cerebral cavernous angiomas are relatively rare vascular malformations that may involve any part of the central nervous system. Cerebral cavernous angiomas are to be distinguished from cerebral arteriovenous malformations. CCMs are venous and not demonstrable by arteriography. Cerebral Cavernous Malformations can lead to stroke, seizures and focal neurological deficits.

Molecular genetics and epidemiology
CCM occurs sporadically and as an autosomal dominant trait. Three genes have been identified for inherited CCM, and mutations in one of these three genes are identified in the majority of CCM families
CCM2 (chromosome locus 7p13)
In 7 unrelated Ashkenazi Jewish patients the same 2-base pair change c.30+5_6delinsTT was characterized

References
Gallione CJ, Solatycki A, Awad IA,Weber J L,. Marchuk DA. A founder mutation in the Ashkenazi Jewish population affecting messenger RNA splicing of the CCM2 gene causes cerebral cavernous malformations. Genet Medicine 2011;13:662-666

Cerebrotendinous xanthomatosis

Autosomal recessive (MIM 213700)
The symptoms as well as the age of onset vary in this disease. Most patients have low intelligence or are mentally retarded. They develop a progressive neurological disease including progressive spasticity with ataxia and in general become incapacitated in the fourth to fifth decade. 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. Juvenile cataracts are frequent and are often the presenting symptom of the disease.
Treatment with cholic acid and chenodeoxycholic acid, pravastatin (another inhibitor of HMG-CoA reductase), or the 2 agents in combination is promising.

Epidemiology:
The disease was found with a relatively high frequency among Jews from Morocco. The incidence was estimated to be 1:10,000 in this community.
In a survey of 250 normal individuals the frequency of the alleles was 0.00658.

Biochemical defect:
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 diagnosis is best based on determination of urinary bile alcohols by mean of gas chromatography. The basic defect is in sterol 27-hydroxylase, a mitochondrial cytochrome P-450.

Molecular genetics:
CYP27 gene (chromosomal locus 2q33-ter)
2 mutations, each with a similar frequency, were demonstrated among Moroccan Jews: a deletion of a thymidine in exon 4 and a G to A transition at the prime site acceptor site of intron 4 ([IVS4DS, G-A, +1] and [1-BP DEL, FS]).
An Ashkenazi Jewsih patient was found to be compound heterozygous [IVS4DS, G-A, +1] [R395H] (M Frydman)

References:
Berginer VM and Abeliovich D. Genetics of cerebrotendinous xanthomatosis: an autosomal recessive trait with high gene frequency in Sepharadim of Moroccan origin. Am J Med Genet 1981;10:151-157.
Leitersdorf E, Reshef A, Meiner V, Levitzki R, Schwartz SP, Dann EJ, Berkman N, Cali JJ, Klapholz L, Berginer VM. Frameshift and splice junction mutations in the sterol 27-hydroxylase gene cause cerebrotendinous xanthomatosis in Jews of Moroccan origin. J Clin Invest 199;91:2488-2493.

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 ichthyosisliver steatosis with hepatomegaly with muscle weakness (myopathy) ataxia, hearing loss subcapsular cataractand sometimes mental retardation. The diagnosis is suspected because of the presence of lipid droplets in granulocytes.

Epidemiology:
The disease was found in several patients of Iraqi Jewish origin.

Molecular genetics:
CGI-58 gene
Unknown among Jews

References:
Dorfman ML, Hershko C, Eisenberg S, Sagher F. Ichthyosiform dermatosis with systemic lipidosis.Arch Dermatol. 1974;110:261-216
Rozenszajn L, Klajman A, Yaffe D, Efrati P. Jordans' anomaly in white blood cells. Report of case. Blood. 1966;28:258-265.

Choreoacanthocytosis

Autosomal recessive (MIM 200150)
Choreoacanthocytosis (CHAC) is a slowly progressive multisystem disorder with involuntary movements, cognitive decline, behavioral changes, seizures, and polyneuropathy.
The mean age at onset is 32 years and the clinical course are usually progressive with cognitive impairment, psychiatric features, and organic personality changes in over half the cases. More than one-third of the cases have seizures. Orofaciolingual involuntary movements and pseudobulbar disturbance commonly caused dysphagia and dysarthria. Chorea was seen in almost all cases, and dystonia, tics, and akinetic-rigid features also occurred.

Epidemiology:
The disease was described in two unrelated patients of Ashkenazi origin and one patient of Iraqi origin.

Molecular genetics:
VPS13A gene (chromosomal locus 9q21)
Each of the Ashkenazi patients was homozygous for [6059delC] mutation and the Iraqi patient for [EX23del] mutation. The mutation [6059delC] was detected in at leat 3 other Ashkenazi alleles (V. Meiner personal communication)

References:
Lossos A, Dobson-Stone C, Monaco AP, Soffer D, Rahamim E, Newman JP, Mohiddin S, Fananapazir L, Lerer I, Linetsky E, Reches A, Argov Z, Abramsky O, Gadoth N, Sadeh M, Gomori JM, Boher M, Meiner V. Early clinical heterogeneity in choreoacanthocytosis.Arch Neurol. 2005;62:611-614.

Chronic granulomatous disease

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. Severe clinical expression was found both in the XLR and AR forms, but in general a milder disease was evident in AR-CGD, particularly in patients with p47(phox) deficiency. Despite early and aggressive therapy, the mortality rate is relatively high. Given that bone-marrow transplantation was successful in five of seven patients, it is recommended to perform it as early as possible before tissue damage is irreversible.

Epidemiology
Autosomal recessive CGDis relatively frequent among Jews from the Caucasian montains and in Jews from Morocco.

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 several families from the Caucasian mountains (Dagestan, Georgia, Azerbaijan), a mutation was found in homozygosity: c.579G>A. One Jewish Dagestan patient was compound heterozygote for G579A and a splice site mutation at intron 2.

CYBA, p22-phox (chromosomal locus 22q13.1). **MIM 601488**
In three consanguineous Morrocan Jewish families a same insertion G after G171 frameshift was characterized.
In a Yemenite consanguineous Jewish family the patient was homozygous for a missense mutation G71A (Gly24 > Glu) also found in an Israeli Arab family.

CYBB GP91-phox (chromosomal locus X21.1). **MIM 306400**
Mutations have been reported in several Jewish families, with a different mutation in each case.

References:
Roos D, de Boer M, Koker MY, Dekker J, Singh-Gupta V, Ahlin A, Palmblad J, Sanal O, Kurenko-Deptuch M, Jolles S, Wolach B. Chronic granulomatous disease caused by mutations other than the common GT deletion in NCF1, the gene encoding the p47phox component of the phagocyte NADPH oxidase. Hum Mutat. 2006;27:1218-1229.

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. Epub 2008 Aug 16.

Chronic hemolysis and childhood relapsing immune mediated polyneuropathy.

Autosomal recessive (MIM)

The patients presented with chronic Coombs' negative hemolysis and relapsing polyneuropathy, presenting as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) The first episode lasted from days to weeks and treatment with intravenous immunoglobulinsand pulse or oral corticosteroids was associated with upper extremities regain of muscle strength. In the following months the course was relapsing, with acute or subacute aggravation of weakness following intercurrent infections. Between episodes, upper limb strength and function was partially regained in a proximal to distal gradient, but there was a progressive muscle wasting involving the feet and the hands and permanent areflexia accompanied by persistent flaccid paralysis of the lower limbs. Few of the exacerbations were accompanied by respiratory insufficiency requiring artificial ventilation. The central nervous system was not involved and the patients' cognitive level was age appropriate. During a typical episode, CRP level was high and blood hemoglobin level dropped to 6-10 Gr% with marked reticulocytosis, negative Coombs` test, increased lactate dehydrogenase level (peak level 1306 IU/L, healthy controls< 260 IU/L) and low haptoglobin, consistent with acute hemolysis. Blood smear revealed polychromasia. The hemolysis was characterized by chronic course with paroxysmal episodes.

Epidemiology:

The disease was reported in 4 North-African origin families (5 of the 8 parents were from Lybia, 2 from Morocco and one from Egypt). The missense mutation, p.Cys89Tyr in CD59, has a carrier rate of 1:66 among Jews of North-African origin.

Molecular genetics:

CD59 gene Chromosomal locus 11p13

A homozygous missense mutation, p.Cys89Tyr was identified in all the patients.

References:

Nevo Y, Ben-Zeev B, Tabib A, Straussberg R, Anikster Y, Shorer Z, Fattal-Valevski A, Ta-Shma A, Aharoni S, Rabie M, Zenvirt S, Goldshmidt H, Fellig Y, Shaag A, Mevorach D, Elpeleg O. CD59 deficiency is associated with chronic hemolysis and childhood relapsing immune mediated polyneuropathy. Blood. 2013;121:129-135

Cohen syndrome

Autosomal recessive (MIM 216550)
The classical features include hypotonia, obesity, preeminent incisors and mental retardation. In a survey thirty-nine patients of 32 families (22 families of Ashkenazi origin) affected by the Cohen syndrome were diagnosed. Although these patients had some general features of Cohen syndrome (e.g., developmental delay, hypotonia, and facial characteristics), they lacked the more specific features of the condition (e.g., neutropenia and retinochoroidal dystrophy) and also had additional features not associated normally with the disease (e.g., height >97th percentile and head circumference >97th percentile).

Epidemiology:
A higher frequency of the syndrome among Ashkenazi Jews was suggested.

Molecular genetics:
COH1 gene Chromosomal locus 8q22-q23
No data on Jewish patients

References:
Sack J, Friedman E. The Cohen syndrome in Israel. Isr J Med Sci 1986 22:766-770.
Kolehmainen J, Wilkinson R, Lehesjoki AE, Chandler K, Kivitie-Kallio S, Clayton-Smith J, Traskelin AL, Waris L, Saarinen A, Khan J, Gross-Tsur V, Traboulsi EI, Warburg M, Fryns JP, Norio R, C M Black G, D C Manson F. Delineation of cohen syndrome following a large-scale genotype-phenotype screen. Am J Hum Genet. 2004; 75:122-127.

Colon cancer predisposition

Autosomal dominant (MIM 175100)
A twofold increased lifetime risk for colorectal cancer is conferred by a mutation in the APC gene. This mutation was found to be frequent among Ashkenazi Jews. The mutation was present in 10 - 28% of the cases among patients with familial colon cancer of Ashkenazi origin.
A similar relative risk was found for carriers of Bloom syndrome among Ashkenazi Jews in one study but was not confirmed in another one.

Epidemiology:
Among healthy Ashkenazi Jewish controls 5-7% carried the I1307K mutation.

Molecular genetics:
APC gene (chromosomal locus 5q21)
I1307K mutation in the APC gene creates a small hypermutable region in the gene and indirectly leads to cancer predisposition.

References:
Cleary SP, Zhang W, Di Nicola N, Aronson M, Aube J, Steinman A, Haddad R, Redston M, Gallinger S, Narod SA, Gryfe R Heterozygosity for the BLM(Ash) mutation and cancer risk. Cancer Res. 2003 63:1769-1771.
Gruber SB, Ellis NA, Rennert G, Offit K, Scott KK, Almog R, Kolachana P, Bonner JD, Kirchhoff T, Tomsho LP, Nafa K, Pierce H, Low M, Satagopan J, Rennert H, Huang H, Greenson JK, Groden J, Rapaport B, Shia J, Johnson S, Gregersen PK, Harris CC, Boyd J. BLM heterozygosity and the risk of colorectal cancer. Science 2002 297:2013.
Laken SJ, Petersen GM, Gruber SB, Oddoux C, Osterer H, Giardiello FM, Hamilton SR, Hampel H, Markowitz A, Klimstra D, Jhanwar S, Winawer S, Offit K, Luce MC, Kinzler KW, Vogelstein B. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nature Genet 1997; 17:79-83.

Color blindness total (achromatopsia)

Autosomal recessive (MIM 216900)
Total color blindness is sometime 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. Funduscopic examination is normal.

Epidemiology:
A relatively high incidence of total color blindness was observed among Jews from Iran and Iraq as well as among Moroccan Jews.

Molecular genetics:
Cone photoreceptor cGMP-gated cation channel CNGA3 (chromosomal locus 2q11)
The missense mutation c.1585G>A, V529M was found in Oriental Jewish families from Iraq, Iran, Buchara, and Afghanistan. The frequency of the mutation in those populations is unknown

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.
Sharon D, Bida L, Greenberg A, Blumenfeld A, Merin S, Rosenmann A, Banin E. A missense CNGA3 mutation which is rare in Western populations is frequent among both Muslim and Oriental Jewish patients with achromatopsia. European Society of Human Genetics congress 2007

Combined oxidative phosphorylation deficiency 3 (COXPD3)

Autosomal recessive (MIM 601538)
In a child of consanguineous Kurdish Jewish parents, the mother reported a paucity of fetal movements throughout pregnancy. At age 36 hours, apathy, irregular breathing, and severe muscular hypotonia were noted. Laboratory investigations revealed severe metabolic acidosis with increased serum lactate level, blood ketone levels, and serum ammonia levels. Echocardiographic examination disclosed severe concentric hypertrophic cardiomyopathy with normal contractility. Death occurred at age 7 weeks

Epidemiology
The disorder was described in one consanguineous Kurdish Jewish family

Molecular genetics
TSFM gene (chromosomal locus 12q13-q14)
All the patients were homozygous for the mutation [C997T].

References
Smeitink JA, Elpeleg O, Antonicka H, Diepstra H, Saada A, Smits P, Sasarman F, Vriend G, Jacob-Hirsch J, Shaag A, Rechavi G, Welling B, Horst J, Rodenburg RJ, van den Heuvel B, Shoubridge EA.Distinct clinical phenotypes associated with a mutation in the mitochondrial translation elongation factor EFTs. Am J Hum Genet. 2006;79:869-877.

Combined pituitary hormone deficiencies (CPHD)

Autosomal recessive (MIM 601538)
In a Moroccan Jewish consanguineous family CPHD was caused by an R120C mutation. The disease was characterized by clinical phenotypic variability in terms of the severity of hormonal deficiencies and the time of their development. The affected exhibited complete gonadotropin deficiency with failure of spontaneous sexual maturation. Adrenocorticotropic hormone deficiency developed in only 2 sisters in the 3rd and 4th decades of life.

Epidemiology
The disorder was described in one Moroccan Jewish consanguineous family

Molecular genetics
PROP-1 gene (chromosomal locus 5q)
All the patients were homozygous for the mutation [R120C].

References
Lazar L, Gat-Yablonski G, Kornreich L, Pertzelan A, Phillip M. PROP-1 gene mutation (R120C) causing combined pituitary hormone deficiencies with variable clinical course in eight siblings of one Jewish Moroccan family. Horm Res. 2003;60:227-231.

Comèl-Netherton syndrome

Autosomal recessive (MIM 256500)

The disorder manifests at birth or soon after and is characterized by a clinical triad which includes localized or generalized ichthyosis, hair shaft abnormalities and atopic diathesis.

Cutaneous manifestations of the syndrome include varying phenotypes ranging from ichthyosis linearis circumflexa, referring to migratory, serpiginous, erythematous plaques bordered by a double-edged scale, up to life-threatening erythrodermic ichthyosis. Pruritus and secondary skin infections are common. Hair abnormalities include trichorrhexis invaginata (bamboo hair), which is pathognomonic for the syndrome, as well as other hair anomalies such as trichorrhexis nodosa, pili torti and alopecia.

Epidemiology

The disorder was described in several Jewish families

Molecular genetics

SPINK5 gene (chromosomal locus 5q32)

The syndrome was reported in three families from Georgia with the mutation c.C2557T in homozygosity in two families and in compound heterozygosity with the mutation c.C649T in the third family. In these families the syndrome was relatively mild with cutaneous manifestions

The mutation c.C649T was found in homozygosity in one family of north European origin and in coupond heterozigosity with c.691delC in another family. The syndrome presented as post natal hypernatremic dehydration, failure to thrive, growth retardation and enteropathy. A family of Iraq origin the patient was homozygous for c.691delC while in a family from Azerbaijan the patient was homozygous for 2240G>81

References

Israeli S1, Sarig O, Garty BZ, Indelman M, Bergman R, Sprecher E, Goldberg I Molecular Analysis of a Series of Israeli Families with Comèl-Netherton Syndrome. Dermatology. 2014;228):183-188

Complement C7 deficiency

Autosomal recessive (MIM 217070)
Individuals with complement C7 deficiency have an increased susceptibility to meningococcal disease.

Epidemiology:
C7 deficiency appears to be relatively frequent among Moroccan Jews. In a random sample of 365 healthy subjects the allele frequency was found to be 1.1%.

Molecular genetics:
C7 (chromosomal locus 5p13)
All the patients of Moroccan Jewish origin examined, shared the same haplotype and had the same mutation p.G1135C

References
Fernie BA, Orren A, Sheehan G, Schleisinger M, Hobart MJ. Molecular bases of C7 deficiency: three different defects. J Immunol 1997;159:1019-1026.
Halle D, Elstein D, Geudalia D, Sasson A, Shinar E, Schlezinger M, Zimran A. High prevalence of complement C7 deficiency among healthy blood donnors of Moroccan Jewish ancestry. Am J Med Genet 2001; 99:325-327.
Zimran A, Rudensky B, Kramer MR, Tedesco F, Ehrenfeld M, Raz R, Greif Z, Gelber M, Lishner M, Golan E, et al. Complement deficiencies in survivors of meningoccocal disease. High prevalence of C7/C8 deficiency in Sepharadic (Moroccan) Jews. Q J Med 1987; 63:349-358.

Cone-rod dystrophy

Autosomal recessive (OMIM 601691)
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 deacrease visual accuty 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 progress, nyctalopia, progressive peripheral visual field deficit and decreasing scotopic ERG are observed.

Molecular genetics and Epidemiology:
ADAM9 gene (chromosomal locus)
In one Tunisian Jewish family, the mutation c.490C>T was found in homozygosity.

References
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; 84:683-691.

Congenital amegakaryocytic thrombocytopenia

Autosomal recessive (MIM 604498)
Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare disorder expressed in early infancy and characterized by isolated thrombocytopenia and megakaryocytopenia with no physical anomalies. In the severe form the patients present with bleeding disorders in early infancy often life threatening. Untreated, many CAMT patients develop aplastic anemia within the first decade of life; the only effective treatment of CAMT is bone marrow transplantation.

Epidemiology and Molecular genetics:
MPL gene (gene location 1p34)
The c.79+2T>A mutation was reported in an Ashkenazi patient the carrier frequency among Ashkenazi Jews is approximately 1:75 (2018 individuals from the ultraorthodox community)

References:
Jalas C, Anderson SL, Laufer T, Martimucci K, Bulanov A, Xie X, Ekstein J, Rubin BY. A founder mutation in the MPL gene causes congenital amegakaryocytic thrombocytopenia (CAMT) in the Ashkenazi Jewish population. Blood Cells Mol Dis. 2011;47:79-83

Congenital disorder of glycosylation type IIk (CGD2K)

Autosomal recessive (MIM 614727)
Three patients belonging to two families presented with a psychomotor-dysmorphism syndrome including postnatal growth deficiency and major spondylo-, epi-, and metaphyseal skeletal involvement. Other features were muscular hypotrophy, fat excess, partial growth hormone deficiency, and, in two of the three patients, episodes of unexplained fever. Additional investigations showed mild to moderate increases of serum transaminases (particularly of aspartate transaminase (AST)), creatine kinase (CK), and lactate dehydrogenase (LDH), as well as decreased coagulation factors VIII, IX, XI, and protein C. Diagnostic work-up revealed a type 2 serum transferrin isoelectrofocusing (IEF) pattern and a cathodal shift on apolipoprotein C-III IEF pointing to a combined N- and O-glycosylation defect.

Epidemiology and Molecular genetics:
TMEM165 gene (gene location 4q12)
The c.792+182G>A mutation was reported in two unrelated Jewish families from Georgia

References:
Foulquier F1, Amyere M, Jaeken J, Zeevaert R, Schollen E, Race V, Bammens R, Morelle W, Rosnoblet C, Legrand D, Demaegd D, Buist N, Cheillan D, Guffon N, Morsomme P, Annaert W, Freeze HH, Van Schaftingen E, Vikkula M, Matthijs G. TMEM165 deficiency causes a congenital disorder of glycosylation. Am J Hum Genet. 2012 ;91:15-26.
Zeevaert R1, de Zegher F, Sturiale L, Garozzo D, Smet M, Moens M, Matthijs G, Jaeken J. Bone Dysplasia as a Key Feature in Three Patients with a Novel Congenital Disorder of Glycosylation (CDG) Type II Due to a Deep Intronic Splice Mutation in TMEM165. JIMD Rep. 2013;8:145-152.

Congenital insensivity to pain with anhidrosis (CIPA)

Autosomal recessive (MIM 256800)

Congenital insensivity 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 is also evident in the cornea leading to traumatic ulcerations and neuro paralytic keratitis. Anihidrosis another prominent feature of the disorder is often associated with recurrent episodes of unexplained fever that can be fatal

Epidemiology:
The disease has been reported in two Moroccan Jewish families from Skoura.

Molecular genetics:
Neurotropic tyrosine kinase receptor 1, NTRK1 (chromosomal locus 1q21-q22)
The mutation c.207-208 delTG was found in homozygosity in the two families but not in a sample of 300 Moroccan Jewish controls.

References:
Suriu C, Khayat M, Weiler M, Kfir N, Cohen C, Zinger A, Aslanidis C, Schmitz G, Falik-Zaccai TC. Skoura - a genetic island for congenital insensitivity to pain and anhidrosis among Moroccan Jews, as determined by a novel mutation in the NTRK1 gene. Clin Genet. 2009;75:230-236.

Congenital hereditary endothelial dystrophies (CHED)

Autosomal recessive (MIM 217700, 217400)
The autosomal recessive form of the congenital hereditary endothelial dystrophies (CHED2) is usually present at birth and nystagmus often develops.

Epidemiology:
The disease has been reported in a sepharadic Jewish family.

Molecular genetics:
Borate transporter SLC4A11 A (chromosomal locus 20p13)
In the family two mutations were found p.Leu808ArgfsX110 and p.Leu843Pro

References:
Desir J, Moya G, Reish O, Van Regemorter N, Deconinck H, David KL, Meire FM, Abramowicz M. Borate transporter SLC4A11 mutations cause both Harboyan syndrome and non-syndromic corneal endothelial dystrophy. J Med Genet 2007;44:322-326.

Corticosterone methyl oxidase II (CMO II) deficiency [congenital hypoaldosteronism]

Autosomal recessive (MIM 124080)
The patients present with a wide spectrum of severity. The most severely affected usually present with dehydration in the first weeks of life - with signs of peripheral vascular collapse including tachycardia, hypotension, gray skin and the clinical picture resembles Addisonian crisis. If untreated, the patients may die in infancy. The children with a less severe disorder tend to present as failure to thrive in the first months of life or later because of retarded growth. The third category of patients may be diagnosed in childhood or even in adult life by screening relatives of the propositus. In these apparent asymptomatic patients in fact a history of postural hypotension, weakness, or salt craving may be obtained; some of them have short stature.
Not only the disorder tends to be milder in older children or adults but also the severity of the disease decreases with age and compensatory mechanisms appear to come in play.

Epidemiology:
The disease was found among Jews from Iran with an incidence of 1:4,000; most of the families originate from Isfahan.

Biochemical defect:
The disease is caused by the deficiency of the enzyme responsible for the final step of the aldosterone biosynthetic pathway: CMO II. Normal levels of aldosterone are found but are inadequate in relation to sodium depletion as indicated by elevated renin activity in plasma. The diagnosis may be done comparing the secretion of aldosterone to the secretion of 18-corticosterone as measured by its urinary metabolites. The ratio of 18-corticosterone metabolites to aldosterone is normally less than 3 and is often greater than 100 in the affected patients.

Molecular genetics:
CYP11B2 (chromosomal locus 8q21)
All the Iranian Jewish patients are homozygous for two linked mutations in the gene CYP11B2: R181W and V386A. Homozygosity for each of the mutations alone does not cause any phenotypic problem.

References:
Cohen T, Theodor R and Rösler A. Selective hypoaldosteronism in Iranian Jews: an autosomal recessive trait. Clin Genet 1977;11: 25-50.
Pascoe L, Curnow KM, Slutsker L, Rösler A, White PC. Mutations in the human CYP11B2 (aldosterone synthetase) gene causing corticosterone methyloxidase II deficiency. Proc Nat Acad Sci 1992; 89:4996-5000.
Rosler A, Rabinowitz D, Theodor R, Ramirez LC, Ulick S. The nature of the defect in a salt-wasting disorder in Jews of Iran. J Clin Endocrinol Metab 1977;44:279-291.

Creutzfeld-Jakob disease

Autosomal dominant (MIM 123400)
In most cases the disease begins after the age of 50 years and lasts less than a year. Prodromal symptoms including asthenia, weight loss or disorders of sleep habits present in one third of the patients.
In approximately half of the patients the onset is manifested only by mental deterioration while some patients present only with physical signs like vertigo, visual or cerebellar disturbances. Other patients present with both types of manifestations at onset. Mental deterioration of dementia, behavioral abnormalities and disorders of high cortical function including aphasia, apraxia or agnosia is noted during the course of the disease in all the affected patients.. Movement disorders are seen in some 90% of the patients and myoclonus is the prominent feature in nearly all. Extrapyramidal symptoms especially profound generalized oppositional rigidity and cerebellar, pyramidal or visual abnormalities are frequently encountered.

Epidemiology:
The disease was found with a relatively high frequency among Jews from Libya, the origin of the families, when known, was Djerba, an island off the coast of Tunisia. The average annual age-adjusted incidence of CDJ among Libyan Jews is 75 cases per million per year, as compared to 0.4 to 1.9 per million population in other ethnic groups in Israel.

Biochemical defect:
The disease can be experimentally transmitted to animals and the infectious pathogen has been isolated and defined as a prion which is a glycoprotein (PrP 27-30) of a molecular weight of 27-30,000 dalton.

Molecular genetics:
PRNP gene (gene location 20 pter-p12)
A point mutation in codon 200 of the PRIP gene [E200K] was demonstrated to be present in all the Libyan Jewish patients with CDJ. The age-specific penetrance of CJD among Libyan-Tunisian Jews carrying the [E200K] mutation, reached 50% at age 60 years and 80% at age 80.

References:
Hsiao K, Meiner Z, Kahana E, Cass C, Kahana I, Avrahami D, Scarlato G, Abramsky O, Prusiner SB, Gabizon R. Mutation of the prion protein in Libyan Jews with Creutzfeld-Jakob disease. New Engl J Med 1991;324:1091-1097.
Kahana E, Alter M, Beraham J and Sofer D. Creutzfeld-Jakob disease: focus among Libyan Jews in Israel. Science 1974;183:90-91.

Cystic fibrosis

Autosomal recessive (MIM 219700)

Epidemiology:
The frequency of cystic fibrosis as well as the distribution of the mutations is different in each of the Jewish communities. While among Ashkenazi Jews, Jews from Libya, Georgia, Greece and Bulgaria the frequency of the disease is in a similar range as in most Caucasian populations (1:2,400), cystic fibrosis is rare in Jews from Yemen (1:8,800), Morocco (1:15,000), Iraq (1:32,000) or Iran (1:39,000).

Molecular genetics:
CFTR gene (chromosomal locus 7q31.2)

TABLE I. Mutations in the CF Bearing Alleles in the Jewish Patients According to the Ethnic Origin

Country of origin	Ashkenazi	Morocco	Tunisia	Balkan	Iraq	Iran/ Kurdistan	Georgia	Yemen	Total
Number of alleles (%)	193 (69.0)	34 (12.1)	12 (4.3)	21 (7.5)	8 (2.8)	3 (0.7)	8 (2.8)	2 (0.7)	281
W1282X (%)	83 (42.8)		1 (8.3)	4 (19.0)					88 (31.3)
ΔF508 (%)	65 (33.5)	24 (70.6)	3 (25.0)	7 (33.3)		1			100 (35.6)
N1303K (%)	10 (5.2)								10 (3.6)
G542X (%)	19 (10.3)			4 (19.0)					24 (8.5)
3849-10 kbC→T (%)	10 (5.1)	1 (2.9)		2 (9.5)					13 (4.6)
1717-1G→A (%)	2 (1.0)								2 (0.7)
D1152H (%)	1 (0.5)								1 (0.4)
S549R (T→G) (%)		4 (11.8)							4 (1.4)
G85E (%)				2 (9.5)					2 (0.7)
405 + 1G→A (%)			8 (66.7)						8 (2.8)
Y1092X (%)					3 (37.5)				3 (1.1)
W1089X (%)				2 (9.5)					2 (0.7)
Q359K/T360K (%)							8 (100)		8 (2.8)
I1234V (%)								2 (100)	2 (0.7)
2751 + 1insT (%)					2 (25.0)				2 (0.7)
3121-1G > A (%)						1			1 (0.4)
M952I (%)					1 (12.5)				1 (0.4)
L165S (%)	1 (0.5)								1 (0.4)
A455E (%)	1 (0.5)								1 (0.4)
L997F (%)		1 (2.9)							1 (0.4)
G1244E (%)		1 (2.9)							1 (0.4)
Unkown (%)	1 (0.5)	3 (8.8)			2 (25.0)	1			7 (2.5)

References:
Abeliovich D, Quint A, Weinberg N, Lerer I, Verchezon G, Lerer I, Ekstein J, Rubinstein E. Cystic fibrosis heterozygote screening in the orthodox community of Ashkenazi Jews: the Dor Yesharim approach and heterozygote frequency. Eur J Hum Genet 1996;4:338-341.

Kerem E, Kalman YM, Yahav Y, Shoshani Z, Abeliovich D, Szeinberg A, Rivlin J, Blau H, Tal A, Ben-Tur L, Springer C, Augarten A, Godfrey S, Lerer I, Branski D, Friedman M, Kerem B. Highly variable incidence of cystic fibrosis and different mutation distribution among different Jewish ethnic groups in Israel. Hum Genet 1995;96:193-197.

Quint A, Lerer I, Sagi M, Abeliovich D. Mutation spectrum in Jewish cystic fibrosis patients in Israel: implication to carrier screening. Am J Med Genet A. 2005; 136:246-268.

Cystinosis

Autosomal recessive (MIM 219800)
In the classical, infantile type of the disease, the age of onset is usually after 6 months and is manifested by failure to thrive, poor eating and excessive drinking and urinating - symptoms which result from renal Fanconi syndrome. The natural history of the disease is dominated by failure to thrive. In addition, the child develops photophobia, and gradually looses renal functions. Clinical rickets is evident. The intelligence is conserved.
In the recent years, specific treatment to reduce the cystine storage, particularly cysteamine, is being tested in addition to the symptomatic therapy to control the severe imbalances and renal transplantation after renal failure appears.
The clinical diagnosis is based on the presence of renal Fanconi syndrome with the presence cystine crystals in bone marrow or/ and in the cornea.

Epidemiology:
The incidence of cystinosis among Jews of North African origin was estimated to be 1:20,000.

Biochemical defect:
There is a massive lysosomal storage of cystine, formed by the oxidation of cysteine to yield the disulfide aminoacid. The lysosomal storage of cystine results from impaired transport of this aminoacid from the interior of the lysosome outside to the cytoplasm. The biochemical diagnosis is based on the increased cystine content in leukocytes which is typically 50 to 100 fold the normal content. Measurement of radioactive cystine retention or counter transport in lysosomes in cultured cells is the basis for the prenatal diagnosis of the disease.

Molecular genetics:
CTNS gene (chromosomal locus 17p13)
The mutation [G339R] has been found in homozygosity in five unrelated Morrocan families. The same mutation has been also detected in patients of other ethnic origin.
A patient of Morocan Jewish origin with a juvenile form of the disease was compound heterozygote [N177T/?]

References:
Gadoth N, Moses SW, Boichis H. Cystinosis in Israel. Harefuah 1975 88:113-114.
Town M, Jean G, Cherqui S, Attard M, Forestier L, Whitemore SA, Callen DF, Gribouval O, Broyer M, Bates GP, van'Hoff W, Antignac C. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. Nature Genet 1998;18:319-324.
Kalatzis V, Cohen-Solal L, Cordier B, Frishberg Y, Kemper M, Nuutinen EM, Legrand E, Cochat P, Antignac C. Identification of 14 novel CTNS mutations and characterization of seven splice site mutations associated with cystinosis. Human Mutation 2002;20:439-446.

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 loss of renal function. The stones may be cystine or uric acid stones.

Epidemiology:
The disease is common worldwide (1:15,000). Its incidence was estimated to be 1:2500 among Jews from Libya.

Biochemical defect:
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.

Molecular genetics:
SLC3A1 gene (chromosomal locus 2p21)
All the patients of Ashkenazi origin had the same mutation in the SLC3A1 gene (C808T).

SLC7A9 gene (chromosomal locus 19q)
A unique mutation was characterized [V170M] among the Jewish patients originating from Libya.

References:
Feliubadalo L, Font M, Purroy J, Rousaud F, Estevill X, Nunes V et al. Non-type I cystinuria caused by mutations in SLC7A9, encoding a subunit ($b^{0,+}$ AT) of rBAT. Nature Genetics 1999;23:52-57.
Pras E, Kochba I Lubetzky A, Pras M, Sidi Y, Kastner DL. Biochemical and studies in Libyan Jewish cystinuria patients and their relatives. Am J Med Genet 1998;80:173-176.
Wartenfeld R, Golomb E, Katz G, Bale SJ, Goldman B, Pras M, Kastner DL, Pras E Molecular analysis of cystinuria in Libyan Jews: exclusion of the SLC3A1 gene and mapping of a new locus on 19q. Am J Hum Genet 1997;60:617-624.
Weinberger A, Sperling O, Rabinovitz M, Brosh S, Adam A, De Vries A. High frequency of cystinuria among Jews of Libyan origin. Hum Hered 1974;24:568-572.

Darier disease

Autosomal dominant (MIM 124000)

Darier disease is a keratinization disorder characterized by loss of adhesion between epidermal cells. Onset is at puberty and fully penetrant in adulthood. The disease is characterized by greasy papules, plaques over seborrheic areas, face, upper trunk and flexures of the extremities. The palms and soles show punctuate keratoses and nail involvement includes sublingual hyperkeratosis and fragility of the edges. Heat and sweating may exacerbate the disease.

Epidemiology:
The disease is relatively common worldwide (1:55,000). The disease was reported in two Ashkenazi families

Molecular genetics
SERCA1-ATP2A2 (chromosomal locus 12q23-24.1)
In each of the families a different mutation was reported [R131X] and [Q177P].

References
Amichai B, Karpati M, Goldman B, Peleg L. Novel mutations in two families with Darier's disease. J Dermatol. 2007;46:64-67.

Deafness, autosomal recessive

Autosomal recessive (MIM 121011)
Among the Ashkenazi Jews it seems that most of the patients with genetic deafness are affected because of a mutation in the GJB2 gene encoding for connexin 26.

Epidemiology:
The disease is common worldwide (1:15,000). Its incidence was estimated to be 1:2500 among Jews from Libya.

Molecular genetics:
GJB2 gene (chromosomal locus 13q11-12)
All the patients of Ashkenazi origin had the same mutation in the SLC3A1 gene (nonsense mutation at position 808).
The frequency of the carriers of the 167delT mutation was estimated to be between 1/10 – 1/25 among Ashkenazi Jews. It was estimated that this mutation is responsible for 70% of all patients with non-syndromic deafness in this community. The high frequency is probably because of a founder effect with genetic drift. Screening of 1012 anonymous Ashkenazi Jewish individuals from the New York Metropolitan area revealed carrier frequencies for 167delT and 35delG of 3.96% (95% CI: 2.75-5.15%) and 0.69% (95% CI: 0.18-1.20%), respectively.
A mutation L205P was found in a Georgian patient with non progressive moderate to profound hearing loss.
Other mutations reported in several cases: 51del112insA and W24X among Bucharian Jews and L90P among Iraqi Jews (Frydman M).
Among several Ashkenazi Jews patients, a deletion mutation in GJB6 gene, coding for connexin 30, was found to be responsible for the deafness, when cooperating with GJB2 mutation in trans. This mutation seems to be frequent also in other populations.

LOXHD1 gene (chromosomal locus 18q12-21)
A premature stop codon (R1572X) was found in patients of Ashkenazi Jewish origin who had severe-profound congenital non-progressive ARNSHL and benefited from cochlear implants. Among 719 anonymous Ashkenazi-Jews four carriers were detected, indicating a carrier rate of 1:180 Ashkenazi Jews

STRC gene (chromosomal locus 15q15.3]
The mutation c.4171C>G (p.R1391G) was found in two Ashkenazi Jewish families with mild deafness.In one family the mutation was found in conpound heterozigosity with a large gene deletion.

TCM1 gene (chromosomal locus 9q13-21)
A founder mutation (p.S647P) was found in patients of Moroccan Jewish origin Among 282 anonymous Moroccan-Jews 16 carriers were detected indicating a carrier rate of 5.7%.

SYNE41 gene (chromosomal locus19q13.11-q13.2)
A founder mutation (c.228delAT) was found in patients of Iraqi Jewish origin Among 157 anonymous Iraqi-Jews 4 carriers were detected indicating a carrier rate of 2.5%.

References:

Brownstein et al. Targeted genomic capture and massively parallel sequencing to identify genes for hereditary hearing loss in Middle Eastern families. Genome Biology 2011

Dong J, Katz DR, Eng CM, Kornreich R, Desnick RJ. Nonradioactive detection of the common Connexin 26 167delT and 35delG mutations and frequencies among Ashkenazi Jews. Mol Genet Metab 2001;73:160-163.

Edvardson S., Jalas C, Shaag A, Zenvirt S, Landau C, Lerer I,.Elpeleg O.
A deleterious mutation in the LOXHD1 gene causes autosomal recessive hearing loss in Ashkenazi Jews. Am J Med Genet 2011;155A:1170-1172

Francey LJ, Conlin LK, Kadesch HE, Clark D, Berrodin D, Sun Y, Glessner J, Hakonarson H, Jalas C, Landau C, Spinner NB, Kenna M, Sagi M, Rehm HL, Krantz ID. Genome-wide SNP genotyping identifies the Stereocilin (STRC) gene as a major contributor to pediatric bilateral sensorineural hearing impairment. Am J Med Genet A. 2012;158A:298-308

Horn HF, Brownstein Z, Lenz DR, Shivatzki S, Dror AA, Dagan-Rosenfeld O, Friedman LM, Roux KJ, Kozlov S, Jeang KT, Frydman M, Burke B, Stewart CL, Avraham KB. The LINC complex is essential for hearing. J Clin Invest. 2013 Jan 25.

Lerer I, Sagi M, Ben-Neriah Z, Wang T, Levi H, Abeliovich D. A deletion mutation in GJB6 cooperating with GJB2 mutation in trans in non-syndromic deafness: a novel founder mutation in Ashkenazi Jews. Hum Mut mutations in brief 2001 458 on line.

Lerer I, Sagi M, Malamud E, Levi H, Raas-Rothshild, Abeliovich D. Contribution of Connexin 26 mutations to non syndromic deafness in Ashkenazi patients and the variable phenotypic effect of the mutation 167delT. Am J Med Genet 2000;95:53-56.

.A novel Lev D, Yannov-Sharav M, Vinkler C, Berman Z, Leshinsky-Silver E missense mutation in the Connexin 26 gene associated with autosomal recessive sensorineural deafness. Hear Res. 2005;202:258-261.

Morell RJ, Kim HJ, Hood LJ et al. Mutations in the connexin 26 gene (GJB2) among Ashknenazi Jews with non syndromic recessive deafness. New Engl J Med 1998;339:1500-1505.

Sobe T, Erlich P, Berry A, Korostichevsky M, Vreugde S, Avraham KB, Bonne-Tamir B, Shochat M. High frequency of the deafness associated 167delT mutation in the connexin 26 (GJB2) gene in Israeli Ashkenazim. Am J Med Genet 1999;86:499-500.

Deafness, autosomal dominant

Molecular genetics and Epidemiology
POU domain class 4 transcription factor 3 gene POU4F3 (MIM 602460)
In one Jewish family originating from Italy with migration to North Africa and Middle East.The patients were heterozygous for [8BP deletion exon 2]

WFS1 (MIM 606201)
In one Ashkenazi Jewish family the patients were heterozygous for [c.2765G>A] (p.E864K)

TECTA (MIM 602574)
In one Turkish Jewish family the patients were heterozygous for [c.5597C>T] (p.T1866M)

References
Brownstein et al. Targeted genomic capture and massively parallel sequencing to identify genes for hereditary hearing loss in Middle Eastern families.
Genome Biol. 2011;12:R89
Vahava O, Morell R, Lynch ED, Weiss S, Kagan ME, Ahituv N, Morrow JE, Lee MK, Skvorak AB, Morton CC, Blumenfeld A, Frydman M, Friedman TB, King MC, Avraham KB. Mutation in transcription factor POU4F3 associated with inherited progressive hearing loss in humans. Science. 1998;279:1950-1954.

Desmin related myopathy

Autosomal dominant (MIM 601419)
The diagnostic criteria include proximal and distal limb muscle weakness often associated with neck, trunk, and velopharynx muscle involvement, associated with cardiac conduction blocks, arrhythmias and restrictive heart failure, and by the presence of numerous desmin reactive aggregates in the muscle fibers, and intrasarcoplasmic accumulation of dense granulofilamentous material on electron microscopy.

Epidemiology
The disorder was described in one Ashkenazi Jewish family

Molecular genetics
Desmin gene (chromosomal locus 2q35)
All the patients were heterozygous for the mutation [L345P].

References
Sjoberg G, Saavedra-Matiz CA, Rosen DR, Wijsman EM, Borg K, Horowitz SH, Sejersen T.A missense mutation in the desmin rod domain is associated with autosomal dominant distal myopathy, and exerts a dominant negative effect on filament formation. Hum Mol Genet. 1999; 8:2191-2198.

Diarrhea, congenital intractable

Autosomal recessive (MIM 251850)
The diarrhea starts in the first 8 days of life, even in breast-fed infants. It is of the secretory type without evidence for a pathogen. All the patients have a jejunal biopsy normal to severe atrophy. All the patients need prolonged total parental nutrition and at the time of the report some were on TNP for 7 years.
The disease is probably autosomal recessive since in one family two siblings were affected and the parents of 3 affected children were consanguineous

Epidemiology:
The disease has been reported in 6 Jewish families all from Iraq.
The patients are homozygous for a16p13.3 deletion
It should be noted that in 1971, 3 affected with Glucose-galactose malabsorption were reported offspring from a consanguineous marriage in an Iraqi-Babylonian Jewish family.

References:
Lebenthal E, Garti R, Mathoth Y, Cohen BE, Katzenelson D. Glucose-galactose malabsorption in an Oriental-Iraqi Jewish family. J Pediat 1971;78: 844-850,
Staussberg R, Shapiro R, Amir J, Yonash A, Rachmel A, Bisset WM, Varsano I. Congenital intractable diarrhea of infancy in Iraqi Jews. Clin Genet 1997;51:98-101.
Bar joseph I, D. Oz-Levi, D. Yagel, T. Olender, E. Ruzzo, A. Alkelai, E. Ben-Asher, H. Reznik-Wolf, B. Pode-Shakked, K. Hartman, R. Shapiro, R. Shamir, R. Kleta, L. Pennacchio, J. Wells, D. Goldstein, E. Pras, D. Lancet, Y. Anikster. Two deletions on chromosome 16p13.3 cause autosomal recessive intractable diarrhea of infancy syndrome ESHG Paris 2013

Disphosphoglycerate mutase deficiency

Autosomal recessive (MIM 222800)
BPGM gene (chromosomal location 7q22-q34)
The disorder was reported in an Iranian (Mashadi) Jewish G6PD deficient individual who had erythrocytosis. The propositus who was the son of first cousin parents was homozygous for c.185C>G (Arg62Gln).

References:
Hoyer JD, Allen SL, Beutler E, Kubik K, West C, Fairbanks VF.Erythrocytosis due to bisphosphoglycerate mutase deficiency with concurrent glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Am J Hematol. 2004; 75:205-208.

Dopa-responsive dystonia

Autosomal dominant (MIM 128230)
There is a 4:1 female predominance in dopa-responsive dystonia GTP cyclohydrolase I activitiy is higher in males than in females, a possible explanation for the difference in frequency of the disorder. The diurnal fluctuations that are characteristic of this disorder may be explained by the relatively short half-life of tetrahydrobiopterin. The family was characterized by variable expressivity and was associated with either a 'classical' DRD phenotype or various atypical phenotypes, such as subtle transitory equinovarus postures of the feet or isolated hand tremor
Tetrahydrobiopterin is an essential cofactor for 3 aromatic amino acid monooxygenases: phenylalanine, tyrosine, and tryptophan hydroxylases. Animals can synthesize tetrahydrobiopterin in vivo from GTP through several enzymatic reactions. The conversion of GTP to D-erythro-7,8-dihydroneopterin triphosphate is the first step in tetrahydrobiopterin biosynthesis, and GTP cyclohydrolase I catalyzes this reaction. This step is thought to be rate-limiting in the pathway.

Epidemiology:
The disorder was described in one Ashkenazi Jewish family

Molecular genetics:
GTP cyclohydrolase I gene (chromosomal locus 14q22.1-q22.2)
The patients were heterozygous for a novel point mutation T94L was characterized.

References:
Markova ED, Slominsky PA, Illarioshkin SN, Miklina NI, Popova SN, Limborska SA, Ivanova-Smolenskaya IA. A novel mutation in the GTP cyclohydrolase I gene associated with a broad range of clinical presentations in a family with autosomal dominant dopa-responsive dystonia. Eur J Neurol. 1999; 6:605-608.

Dubin Johnson syndrome (DJS)

Autosomal recessive (MIM 237500)
Chronic or intermittent jaundice is the most common finding in patients with Dubin Johnson syndrome (DJS). The onset has been observed in infancy or late in adulthood but is generally between the age of 15 to 35 years. Many factors may precipitate or aggravate jaundice such as infection or pregnancy. Many of the patients complain of vague abdominal pains, some with weakness, occasional nausea, vomiting and or recurrent diarrhea. In about half the patients the liver is enlarged, and is tender in some.
The finding of chronic idiopathic hyperbilirubinemia (conjugated, direct) with typical pigmentary changes in liver biopsy, are the criteria for diagnosis of DJS.
Association with factor VII deficiency:
Some of the patients have bleeding symptoms. It was demonstrated that deficiency or decreased levels of factor VII is found with a higher frequency among patients with DJS than in the general population. There is not yet a good explanation for this observation.

Epidemiology:
The disease has been reported to occur mostly in individuals from Iran and its incidence was calculated to be 1:1,300 in this group; most of the families originate from Isfahan. While the disease is rare among Ashkenazi Jews 1: 100,000, its incidence is higher in other groups like Jews from Iraq and Morocco.

Molecular genetics:
Multidrug resistance protein 2 MRP2 (chromosomal locus 10q24)
All the Iranian Jewish patients are homozygous for the mutation I1173F with a same founder haplotype. Heterozygosity was found in 14/243 examined (5.8%) and the allele frequency is 2.9% (95% confidence interval 1.6 to 4.8%).
All the Moroccan Jewish patients are homozygote for a mutation [R1150H] with a same founder haplotype. Heterozygosity was found in 1/226 examined (1.8%) and the allele frequency is 0.9% (95% confidence interval 0.24 to 2.27%).
A founder mutation IVS8+4a>G was found among the Ashkenazi patients with a carrier prevalence of 0-0.082% (no carriers among 450 individuals)

References:
Mor-Cohen R, Zivelin A, Rosenberg N, Shani M, Mualem S, Seligsohn U. Identification and functional analysis of two novel mutations in the multidrug resistance protein 2 gene in Israeli patients with Dubin Johnson syndrome. J Biol Chem 2001; 276:36923-36930.
Mor-Cohen R, Zivelin A, Rosenberg N, Goldberg I, Seligsohn U. A novel ancestral splicing mutation in the multidrug resistance protein 2 gene causes Dubin-Johnson syndrome in Ashkenazi Jewish patients. Hepatol Res. 2005; 31:104-111
Shani M Seligsohn U Gilon E Sheba C, Adam A. Inheritance of the Dubin Johnson syndrome. New Engl J Med 1973; 288:113-117.

Dyggve-Melchior-Clausen syndrome

Autosomal recessive (MIM 224230)
Dyggve-Melchior-Clausen syndrome (DMC) is characterized by the association of a spondylo-epi-metaphyseal dysplasia and mental retardation. The spine showed generalized platyspondyly. Irregularities of the iliac crest gave an appearance of a lace border around it. There is a characteristic double hump with central constriction of the vertebral bodies which is present at age 4 years and becomes more distinct in late childhood. In adult patients, the vertebral bodies become more rectangular as the appositional bone which appears during adolescence becomes fused.

Molecular genetics and epidemiology:
DYM gene (chromosomal locus 18q12-q21.1)
In a Moroccan Jewsih family six out of 10 sibling were affected. No molecular studies have been reported.

References:
Schorr S, Legum C, Ochshorn M, Hirsch M, Moses S, Lasch EE, El-Masri M. The Dyggve-Melchio-Clausen syndrome. AJR Am J Roentgenol. 1977; 128:107-113.

Dysautonomia, familial

Autosomal recessive (MIM 223900)
The disease is due to a disturbance of autonomic and peripheral sensory functions. The main clinical manifestations are prominent in infancy. Most of the symptoms are secondary to anomalies in the autonomic nervous system, including excessive salivation and sweating, absence of tears and diminished corneal reflex, vasomotor instability with labile blood pressure and skin blotching, defective temperature control and episodic fever. Symptoms also include feeding problems in part since the swallowing is poorly coordinated and lead to gapping, vomiting and aspirations. The clinical manifestation of peripheral sensory dysfunction is diminished or absence of pain leading to repeated trauma and corneal ulcerations. Deep tendon reflexes are diminished or absent. Pulmonary infections are frequent secondary to recurrent aspirations and excessive secretions and lead to pulmonary failure in many of the affected children.
The diagnosis is based on clinical findings; the absence of fungiform papillae and taste buds in tongue is pathognomonic for the disease. The histamine test, in which the pain is reduced and there is no axon flare after intradermal injection of histamine phosphate, is a very useful tool for diagnosis. Another diagnostic test is the response of the pupil to metacholine which induces myosis in children affected with dysautonomia instead of no change in non affected children.

Epidemiology:
The disease is found almost exclusively among Ashkenazi Jews, the incidence in this community was calculated to be 1:3700. The carrier frequency is 1/36 among the Ashkenazi Jews according to molecular studies.

Molecular genetics:
IKBKAP gene (chromosomal locus 9q31)
A splicing mutation in the IKBKAP gene resulting in skipping of exon 20 was found in 99.5% of the patients. Another mutation R696P was found in few other patients.

References:
Anderson SL, Coli R, Daly IW, Kichula A, Rork MJ, Volpi SA, Ekstein J, Rubin BY. Familial dysautonomia is caused by mutations of the IKAP gene. Am J Hum Genet 2001;68:753-758
Maayan C, Kaplan E, Shachar S, Peleg O, Godffrey S. Incidence of familial dysautonomia in Israel 1977-1981. Clin Genet 1987; 32:106-108.
Slaugenhaupt S A, Blumenfeld A, Gill S, Leyne M, Mull J, Cuajungco MP, Liebert C. B, et al. Tissue specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet 2001; 68:598-605.

Dyserythropoietic anemia type II, Congenital

Autosomal recessive (MIM 224100)
Congenital dyserythropoietic anemias (CDA) are a rare group of red blood cell disorders of unknown etiology characterized by ineffective erythropoeisis, pathognomonic cytopathology of the nucleated red blood cells in the bone marrow and secondary hemochromatosis. Three types have been delineated; type II is the most common characterized by normocytic binuclear or multinuclear red cells, which on electron microscopy contain double cytoplasmic membranes.
The 11 Jewish patients presented with anemia and all needed splenectomy. In three patients a severe anemia was present in the neonatal period. None of the patients was transfusion dependent, three needed deferoxamine treatment and two of the patients had clinical hemochromatosis.

Epidemiology:
The disease has been diagnosed among 11 patients from 7 Moroccan Jewish families and one Algerian/Moroccan family. The mutation c.325G>A was found in 1 out 102 Moroccan Jews.

Molecular genetics:
SEC23B gene (chromosomal locus20p11.2)
Homozygozity for the same mutation [c.325G>A; p.Glu109Lys] was found in all the patients but one who was compound heterozygote for this mutation and [pThr710Met].

References:
Amir A, Dgany O, Krasnov T, Resnitzky P, Mor-Cohen R, Bennett M, Berrebi A, Tamary H. E109K Is a SEC23B Founder Mutation among Israeli Moroccan Jewish Patients with Congenital Dyserythropoietic Anemia Type II. Acta Haematol. 2011; 125:202-207.

Dyskeratosis congenita

Autosomal dominant (MIM 300240)

TERT gene (chromosomal locus 5p15.33)
In a family of Iraqi Jewish origin clinical features compatible with a dominant form of the disease all the affected males presented with isolated thrombocytopenia that was followed by decreased RBC and/or WBC counts. Anticipation for aplastic anemia, premature greying of hair, pulmonary fibrosis and hepatic fibrosis was observed. In 2 patients, cardiac abnormalities were detected: cardiac and cardiomegaly. Death was due to respiratory failure or hepatic failure; one patient died as a result of myocardial infarction.While all 6 males in the family were severely affected, neither of the 2 females showed overt clinical manifestations of the disease except for premature grey hair in both and borderline RBC count in one of them. A novel heterozygous missense mutation (c.1892 G>A; p.Arg631Gln), was detected in all the patients

References:
Basel-Vanagaite L, Dokal I, Tamary H, Avigdor A, Garty BZ, Volkov A, Vulliamy T.Expanding the clinical phenotype of autosomal dominant dyskeratosis congenita caused by TERT mutations. Haematologica. 2008 93:943-944

Dyskeratosis congenital autosomal recessive- Hoyerall-Hreidarsson syndrome

Autosomal recessive (MIM 300240)
Hoyeraal-Hreidarsson syndrome is similar to autosomal recessive dyskeratosis congenita-5 characterized by onset of bone marrow failure and immunodeficiency in early childhood. Most patients also have growth and developmental delay and cerebellar hypoplasia.

Molecular genetics and epidemiology:
RTEL1 gene (chromosomal locus 20q13.33)
In two Ashkenazi Jewish families the patients were homozygous for a founder mutation R1264H. in another Ashkenazi Jewish family the patients were compound heterozygote for c.C2920T and c.G1476T. The frequency of the mutation was not deternimed

TERT gene (chromosomal locus 5p15.33)
In a consanguineous Iranian Jewish family a female patient was homozygous for p.Arg901Trp (R901W).

References:
Ballew BJ, Joseph V, De S, Sarek G, Vannier JB, Stracker T, Schrader KA, Small TN, O'Reilly R, Manschreck C, Harlan Fleischut MM, Zhang L, Sullivan J, Stratton K, Yeager M, Jacobs K, Giri N, Alter BP, Boland J, Burdett L, Offit K, Boulton SJ, Savage SA, Petrini JH. A Recessive Founder Mutation in Regulator of Telomere Elongation Helicase 1, RTEL1, Underlies Severe Immunodeficiency and Features of Hoyeraal Hreidarsson Syndrome. PLoS Genet. 2013;9
Deng Z, Glousker G, Molczan A, Fox AJ, Lamm N, Dheekollu J, Weizman OE, Schertzer M, Wang Z, Vladimirova O, Schug J, Aker M, Londoסo-Vallejo A, Kaestner KH, Lieberman PM, Tzfati Y.Inherited mutations in the helicase RTEL1 cause telomere dysfunction and Hoyeraal-Hreidarsson syndrome. Proc Natl Acad Sci U S A. 2013;1103408-1103416.
Marrone A, Walne A, Tamary H, Masunari Y, Kirwan M, Beswick R, Vulliamy T, Dokal I. Telomerase reverse-transcriptase homozygous mutations in autosomal recessive dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome. Blood. 2007;110:4198-4205.

Dystonia primary torsion

Autosomal recessive (MIM)

Three siblings had childhood onset of limb dystonia, and slow progression to generalized dystonia with predominant cranio-cervical involvement. There were no other abnormal signs, apart from dystonia and jerky tremor over a 12-year follow-up. All investigations for other causes of primary and secondary dystonia had normal results

Epidemiology
The disorder was described in one Iranian Jewish family

References
Khan NL, Wood NW, Bhatia KP. Autosomal recessive, DYT2-like primary torsion dystonia: a new family. Neurology. 2003; 61: 1801-1803.

Ectodermal dysplasia ectrodactyly and macular dystrophy

Autosomal recessive (MIM 601553)
Hypotrichosis with juvenile macular dystrophy (HJMD) and ectodermal dysplasia, ectrodactyly and macular dystrophy (EEM) are both caused by mutations in the CDH3 gene. There is a phenotypic continuum between HJMD and EEM.

Epidemiology:
The syndrome was reported in one Jewish family of Yemmenite origin

Molecular genetics:
CDH3 gene encoding P cadherin (chromosomal locus 16q22.1)
The patients were homozygous for p.G277V

References
Basel-Vanagaite L, Pasmanik-Chor M, Lurie R, Yeheskel A, Kjaer KW. CDH3 related syndromes reports ona new mutation and overview of the genotype phenotype correlations. Mol Syndromology 2010;1:223-230.

Ehlers-Danlos syndrome type VII-C

Autosomal recessive (MIM 225410)
The patients present with extreme fragility of the skin, other symptoms include blue sclerae and soft, velvety, hyperextensible skin. Marked bruising and open wounds following minor trauma are present, the excised skin can be torn by hand.

Epidemiology:
The disease has been diagnosed among in several Ashkenazi Jewish families In one family in which the origin was determined the grand parents were from Belarus

Molecular genetics:
ADAMTS2 gene (chromosomal locus 5q23)
Homozygozity for the same mutation [Q225X] was found in all the Ashkenazi Jewish patients.

References:
Colige A, Sieron AL, Li SW, Schwarze U, Petty E, Wertelecki W, Wilcox W, Krakow D, Cohn DH, Reardon W, Byers PH, Lapiere CM, Prockop DJ, Nusgens BV.Human Ehlers-Danlos syndrome type VII C and bovine dermatosparaxis are caused by mutations in the procollagen I N-proteinase gene. Am J Hum Genet. 1999;65:308-317.

Bar-Yosef O, Polak-Charcon S, Hoffman C, Feldman ZP, Frydman M, Kuint J. Multiple congenital skull fractures as a presentation of Ehlers-Danlos syndrome type VIIC. Am J Med Genet A. 2008;146A:3054-3057.

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 Ashkenazi Jewish families

Molecular genetics:
NR2E3 gene (chromosomal locus 15q23)
A same mutation [c.923G>A] was found in several Ashkenazi Jewish patients but was not found in 111 Ashkenazi controls. The same mutation was found in Crypto-Jews (Marranos) from Belmonte in the Beira-Baixa province of Portugal. Those were survivors of Spanish Jews who were persecuted in the late fifteenth century and escaped to Portugal where they were forced to convert to save their lives. One of Jewish patient from Morocco who was homozygous for the same mutation was diagnosed as retinitis pigmentosa.
One Ashkenazi Jewish patient was compound heterozygous for the common mutation and [c.747+1G>C]. One patient Tunisian/Ashkenazi was also compound heterozygous for the Ashkenazi mutation and c.194-202 del9bp]

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.
Wright AF, Reddick AC, Schwartz SB, Ferguson JS, Aleman TS, Kellner U, Jurklies B, Schuster A, Zrenner E, Wissinger B, Lennon A, Shu X, Cideciyan AV, Stone EM, Jacobson SG, Swaroop A. Mutation analysis of NR2E3 and NRL genes in Enhanced S Cone Syndrome. Hum Mutat. 2004; 24:439.

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 clasically 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.

Molecular genetics:
Keratin K5
Several mutations were characterized in Ashkenazi Jewish patients [K199R] [V324D] [E167K] [H1635delG] [L311P]
Keratin K14
Several mutations were characterized in Ashkenazi Jewish patients [A134P] [A125C] [V270M] [Q369X] [R388H]

References:
Abu Sa'd J, Indelman M, Pfendner E, Falik-Zaccai TC, Mizrachi-Koren M, Shalev S, Amitai DB, Raas-Rothshild 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.
Rugg EL, Baty D, Shemanko CS, Magee G, Polak S, Bergman R, Kadar T, Boxer M, Falik-Zaccai T, Borochowitz Z, Lane EB. DNA based prenatal testing for the skin blistering disorder epidermolysis bullosa simplex. Prenatal Diag 2000; 20:371-377.

Epidermolysis bullosa, generalized atrophic benign

Autosomal recessive (MIM 22665)
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.

Molecular genetics:
COL7A1 (chromosomal locus 10q24.3)
Several mutations were characterized in Ashkenazi Jewish patients [6652-2A>G] [G2079R] [628+1G>A] [G2067R] [G2031S] [2528delA]

References:
Abu Sa'd J, Indelman M, Pfendner E, Falik-Zaccai TC, Mizrachi-Koren M, Shalev S, Amitai DB, Raas-Rothshild 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.

Molecular genetics:
Epidermolysis bullosa lethalis is caused by mutations in any 1 of the 3 polypeptides of laminin-5:
alpha-3 (LAMA3)
beta-3 (LAMB3)
Two mutations were characterized in Ashkenazi Jewish patients [2528delA] and [R42X]
gamma-2 (LAMC2)

References:
Abu Sa'd J, Indelman M, Pfendner E, Falik-Zaccai TC, Mizrachi-Koren M, Shalev S, Amitai DB, Raas-Rothshild 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.

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 Jewish family of Moroccan origin 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 Moroccan Jewish family the mutation was 2030-2031insT in all the patients.

References:
Dibbens LM, Tarpey PS, Hynes K, Bayly MA, Scheffer IE, Smith R, Bomar J, Sutton E, Vandeleur L, Shoubridge 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, Gécz 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, Szepetowski 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.

Erythrokeratodermia variabilis

Autosomal dominant (MIM 133200)
Erythrokeratodermia variabilis is a rare genodermatosis characterized by the coexistence of areas of erythema usually transient and migratory and fixed keratotic lesions.

Molecular genetics:
Connexin 30.3(chromosome location:1p34-35)
In a Jewish family, of Kurdish origin, with EKVF a heterozygous T-->C transition leading to the missense mutation (F137L) was characterized

References:
Hacham-Zadeh S, Even-Paz Z. Erythrokeratodermia variabilis in a Jewish Kurdish family.Clin Genet. 1978; 13: 404-408.
Macari F, Landau M, Cousin P, Mevorah B, Brenner S, Panizzon R, Schorderet DF, Hohl D, Huber M. Mutation in the gene for connexin 30.3 in a family with erythrokeratodermia variabilis. Am J Hum Genet. 2000; 67:1296-1301

Factor V and factor VIII combined deficiency

Autosomal recessive (MIM 227300)
The patients affected with this bleeding disorder are most commonly noted because of excessive bleeding after surgical trauma and deliveries. Spontaneous bleeding is also frequent in these patients and epistaxis, gingival bleeding, hematuria and gastrointestinal bleeding are observed infrequently. All the women have menorrhagia. The diagnosis is based on the finding of low levels of factors V and VIII (range 5-30% of normal).

Epidemiology:
The disease is very rare and has been reported in very few families all over the world. However, many of the reported families were Oriental or Sepharadic Jews; and the incidence of the disease in non-Ashkenazi Jews was calculated to be 1:100,000 live births. The disease has not been reported yet in Ashkenazi Jews.

Molecular genetics:
LMAN1 gene (chromosomal locus 18q21.3-22)
The gene LMAN1 is a component of the ER-Golgi intermediate compartment. All the Jewish patients from Tunisia have a thymidine (T) to cytosine (C) transition in intron 9 at a donor splice [IVS383 DS, 5C+2] site found on the same haplotype (at least 6 cM) and in patients from Iraq, Iran and Egypt a guanine (G) insertion in exon 1 [Ibp IN86GG] found on another haplotype (less than 1 cM).
Since all affected Tunisian families belong to the ancient Jewish community in the island of Djerba off the coast of Tunisia, members of this community were screened for the intron 9 T <-- C transition. Among 233 apparently unrelated individuals five heterozygotes were detected, predicting an allele frequency of 0.0107 (95% confidence interval, 0.0035-0.0248), while among 259 North African Jews none was found to carry the mutation.
The G insertion in exon 1 was found in one of 245 Iraqi Jews, predicting an allele frequency of 0.0022 (95% confidence interval, 0.0001-0.0123), but in none of 180 Iranian Jews examined.

References:
Nichols WC, Seligsohn U, Zivelin A, Terry VH, Hertel CE, Wheatley MA, Moussalli MJ, Hauri HP, Ciavarella NM, Kaufman RJ, Ginsburg D. Mutations in the ER-Golgi intermediate compartment protein ERGIC-53 cause combined deficiency of coagulation factors V and VIII. Cell 1998; 93:61-70.
Seligsohn U, Zivelin A, Zwang E. Combined factor V and factor VIII deficiency among non-Ashkenazi Jews. New Engl J Med 1982; 307:1191-1195.
Segal A, Zivelin A, Rosenberg N, Ginsburg D, Shpilberg O, Seligsohn U.A mutation in LMAN1 (ERGIC-53) causing combined factor V and factor VIII deficiency is prevalent in Jews originating from the island of Djerba in Tunisia. Blood Coagul Fibrinolysis. 2004; 15:99-102.

Factor VII deficiency

Autosomal recessive (MIM 227500)
Some of the patients have bleeding symptoms.
It was demonstrated that deficiency or decreased levels of factor VII is found with a higher frequency among patients with Dubin Johnson syndrome than in the general population. There is no good explanation for this observation.

Epidemiology:
The deficiency has been reported to occur mostly in individuals from Iran and from Morocco. The incidence of the mutation A244V is 1:40 and 1:42 respectively.

Molecular genetics:
Factor VII gene (chromosomal locus 13q34)
All patients from Morocco or Iran have the same mutation [Ala244Val] that was observed also in patients from other origins.

References:
Tamary H, Fromovich Y, Shalmon L, Reich Z, Dym O, Lanir N, Brenner B, Paz M, Luder AS, Blau O, Korostishevsky M, Zaizov R, Seligsohn U. Ala244val is a common probably ancient mutation causing factor VII deficiency in Moroccan and Iranian Jews. Thromb Haemost 1996; 76:283-291.

Factor XI deficiency (PTA).

Autosomal recessive (MIM 264900).
The affected patients present with a general mild bleeding tendency which is often diagnosed after trauma, a dental or a surgical procedure. Some of the patients also present spontaneous bleeding like hemarthrosis or purpura.
It should be noted that some 25% of the patients have excessive bleeding after circumcision. Childbirth is accompanied with relatively few problems.

Epidemiology:
Among the Ashkenazi Jews the incidence of factor XI deficiency has been estimated to be 1:190. It is also relatively frequent in Jews from Iraq (allele frequency 0.0167). Because of the high frequency of the disorder, it is recommended to screen for factor XI deficiency in all Ashkenazi Jews before any major surgery.

Biochemical defect:
Deficiency of factor XI coagulant activity.

Molecular genetics:
Factor XI gene (chromosomal locus 4q35)
Two different mutations in the cDNA of the factor XI gene have been found to be frequent among Ashkenazi Jews, each in a similar frequency:

-a nonsense mutation in exon 5: GAA coding for Glu-117 is changed to a stop codon TAA (type II mutation) [allele frequency 0.0217].

-a missense mutation in exon 9, TCC coding for Phe-283 is changed to TCT coding for leucine (type III mutation) [allele frequency 0.0167].

Type II mutation is also found among Iraqi Jews (similar haplotype).
Another mutation (TypeI) has been found in several Ashkenazi Jewish families IVS14+1 G>A. It represents a relatively recent mutation that is rare among Ashkenazi Jews.

References:
Asakai R, Chung DW, Ratnoff OD, Davie EW. Factor XI (plasma thromboplastin antecedent) deficiency in Ashkenazi Jews is a bleeding disorder that can result from three types of point mutations. Proc Natl Acad Sci 1989;86: 7667-7671.
Asakai R, Chung DW, Davie EW, Seligsohn U. Factor XI deficiency in Ashkenazi Jews in Israel. New Engl J Med 1991; 325:153-158.
Seligsohn U. High gene frequency of factor XI (PTA) deficiency in Ashkenazi Jews. Blood 1978; 51: 1223-1228.

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 and Molecular genetics:
The gene for the A1 subunit of FXIII, F13A1 (chromosomal locus 6p25).
The disorder has been reported in one Ethiopia Jewish patient compound heterozygote for 10bp deltion in exon 12 (1652-1661 and Ala318Val and one Jewish patient of Indian origin homozygous for [IVS11+1]

References:
Vysokovsky A, Saxena R, Landau M, Zivelin A, Eskaraev R, Rosenberg N, Seligsohn U, Inbal A. Seven novel mutations in the factor XIII A-subunit gene causing hereditary factor XIII deficiency in 10 unrelated families. J Thromb Haemost 2004; 2:1790-1797.

Familial amyloid polyneuropathy

Autosomal dominant (MIM 176300)
In a three-generation family of Jewish-Yemenite origin the affected individuals had sensorimotor and autonomic neuropathy and cardiomyopathy accompanied by prominent dysphagia, hearing loss and asymptomatic carpal tunnel syndrome. Brain MRI in the proband showed multifocal white matter lesions.

Epidemiology:
The disease has been reported in one largeYemenite Jewish family.

Molecular genetics:
Transthyretin (chromosomal location 18q11.2 q12.1)
The Tyr77 was found in affected patients

References:
Lossos A, Soffer D, Steiner-Birmanns B, Hassin-Baer S, Sadeh M, Sagi M, Linetski E, Abramsky O, Argov Z, Rosenmann H.Extended phenotype in the transthyretin Tyr77 familial amyloid polyneuropathy. Eur Neurol. 2005;53:55-59.

Familial cold autoinflamatory syndrome

Autosomal dominant (MIM 120100)
Familial cold autoinflamatory syndrome is a rare condition that is characterized by recurrent episodes of cold induced urticarial wheals often associated with joint pain and swelling, fever and chills.

Epidemiology:
The disease has been reported in one Ethiopian Jewish family.

Molecular genetics:
CIAS1 (chromosome location 1q44)
A novel mutation, F525C was identified in one Ethiopian Jewish family.

References:
Shalev SA, Sprecher E, Indelman M, Hujirat Y, Bergman R, Rottem M. A Novel Missense Mutation in CIAS1 Encoding the Pyrin-Like Protein, Cryopyrin, Causes Familial Cold Autoinflammatory Syndrome in a Family of Ethiopian Origin. Int Arch Allergy Immunol. 2007; 143:190-193

Familial hyperekplexia

Autosomal recessive (MIM 231040)
Hyperekplexia is a rare disorder characterized by an exaggerated startle response to noise and handling and by neonatal hypertonia. It is predominantly an autosomal dominant disease; however, atypical cases with additional variable manifestations have been reported. Ttwo siblings born after an uneventful pregnancy had increased startle and tone from birth and later became hypotonic. A metabolic evaluation, including a muscle biopsy, was normal. At the age of 18 months and 12 months, respectively, they developed status epilepticus refractory to all treatment that culminated in death. An autopsy in the girl did not reveal any brain pathology.

Epidemiology:
The disease has been reported in one Ashkenazi Jewish family.

Molecular genetics:
Unknown

References:
Lerman-Sagie T, Watemberg N, Vinkler C, Fishhof J, Leshinsky-Silver E, Lev D. Familial hyperekplexia and refractory status epilepticus: a new autosomal recessive syndrome. J Child Neurol 2004; 19:522-525.

Familial Medullary thyroid carcinoma

Autosomal recessive (MIM 155240)

Molecular genetics:
RET proto oncogene (chromosomal locus 10q11.2)
In two Moroccan Jewish families with familial medullary thyoid carcinoma and Hisrchsprung disease, the mutation Cys 618Arg cosegregated with the disease.

References:
Peretz H, Luboshitsky R, Baron E, Biton A, Gershoni R, Usher S, Grynberg E, Yakobson E, Graff E, Lapidot M. Cys 618 Arg mutation in the RET proto-oncogene associated with familial medullary thyroid carcinoma and maternally transmitted Hirschsprung's disease suggesting a role for imprinting. Hum Mutat. 1997; 10:155-159.

Familial Mediterranean Fever

Autosomal recessive (MIM 249100)

The disease is characterized by short periodic attacks of fever and painful manifestations in the abdomen, chest, joints or skin.. 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 as usually it is preceded by pain. Most attacks last for 12 to 24 hours. Some are longer, in particular when the joints are involved. The abdominal crises are the most common and dramatic form of the attacks, cause an acute like abdomen, and often the patients 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 monoarticular, 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. Leukocytes may be found in the synovial fluid, 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 significant complication of the disease is the development of amyloidosis, which occurs among North African Jews.. Amyloid nephropathy is independent of the severity of the other signs of the disease and may appear at early age. The manifestations consist of protenuria, nephrotic syndrome and renal failure.

Treatment with colchicine reduces the symptoms and the frequency of the periodic attacks and may prevent the development of amyloidosis.

The disease also exists in Ashkenazi Jews but it seems that the clinical symptoms are milder. Several patients even present spontaneous remissions.

Epidemiology:

The disease is found with a relatively high incidence in Jews from the Mediterranean countries. The highest frequency occurs among Jews from Libya (1:5 carriers), Algeria, Tunisia and Morocco (1:6.5 carriers). It is also frequent among Jews from Iraq and Turkey (1:13 carriers).

The disease has also been reported among Ashkenazi Jews but its frequency is not clear and the carrier frequency was estimated to be 1/11-1/135 in different studies. In a molecular analysis of 213 anonymous Ashkenazi Jews, the overall frequency of the known mutations was 21% (E148Q = 0.104, P369S = 0.045, K695R = 0.030 and V726A = 0.043). The high frequency of carriers opposed to the incidence of the disease suggests a reduced penetrance in this population. Another possibility may be that the E148Q mutation is a polymorphism. A dominant inheritance of the disease was proposed to explain a vertical inheritance in several families among Ashkenazi Jews. However, it was demonstrated that this observation is secondary to the high frequency of the disease in this population.

Molecular genetics:

MEFV gene (chromosomal locus 16p13.3)

Few mutations are responsible for the high frequency of the disease (M694V, V726A, M680I, M694I and E148Q). There is a significant linkage disequilibrium for all the major mutations in all the populations suggesting that they are ancient. Among the North African Jews one mutation M694V is predominant (more than 90% of the mutations); among the Iraqi Jews M694V and V726A are both frequent. Another mutation E148Q is frequent in these communities as well among Ashkenazi Jews.

In rule, homozygotes for the M694V mutation and the complex V726A-E148Q allele are the most severely affected often with renal amyloidosis. M694V homozygotes have a severe form of the disease. Mutations E148Q and V726A have reduced penetrance. Homozygotes for the M680I or V726A alleles and compound heterozygotes for either the M694V or the V726A-E148Q alleles in combination with the E148Q, the V726A or the M680I alleles are significantly less severely affected.

In a group of Iranian Jewish patients the frequent mutations were not found. In three unrelated alleles a new mutation G632S was characterized (10% of the alleles) that is associated with a mild phenotype. A rare mutation R653H was found in one allele.

References:

Aksentijevich I, Yelizaveta , Samuels J, Centola M, Pras E, Chae JJ, Oddoux C, Wood G, Azzaro MP, Palumbo G, Giustolisi R, Pras M, Ostrer H , Kastner DL. Mutation and haplotype studies of Familial Mediterranean Fever reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population. Am J Hum Genet 1999; 64:949-62.

Bernot A, da Silva C, Petit JL, Cruaud C, Caloustian C, Castet V, Ahmed-Arab M, Dross C, Dupont M, Cattan D, Smaoui N, Dode C, Pecheux C, Nedelec B, Medaxian J, Rozenbaum M, Rosner I, Delpech M, Grateau G, Demaille J, Weissenbach J, Touitou I. Non-founder mutations in the MEFV gene establish this gene as the cause of familial Mediterranean fever. Hum Mol Genet 1998; 7:1317-1325.

Daniels M, Sohat T, Brenner-Ullman, Shohat M. Familial Mediterranean fever: high gene frequency among the non-Ashkenazi and Ashkenazic Jewish populations in Israel. Am J Med Genet 1995; 55:311-314.

Gershoni-Baruch R, Brik R, Shinawi M, Livneh A. The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever. Eur J Hum Genet. 2002 10:145-199.

Sohar E, Gafni J and Pras M, Heller H. Familial Mediterranean fever: a survey of 470 cases and review of the literature. Amer J Med 1967; 43:227-253.

Shinar Y, Kuchuk I, Menasherow S, Kolet M, Lidar M, Langevitz P, Livneh A.Unique spectrum of MEFV mutations in Iranian Jewish FMF patients clinical and demographic significance. Rheumatology (Oxford). 2007; 46:1718-1722.

Familial Adenomatous Polyposis (juvenile, type2)

Autosomal recessive (MIM 608558)
Colorectal adenomatous polyposis is a disorder characterized by adult-onset of multiple colorectal adenomas and adenomatous polyposis. Affected individuals have a significantly increased risk of colorectal cancer

Molecular genetics:
MUTYH (chromosome 1p34)
Two mutationsY179C and G396D that are frequent in all the populations were also found in families of Moroccan Jewish origin

References:
Rosner G, Rozen P, Bercovich D, Shochat C, Solar I, Strul H, Kariv R, Halpern Z. A protocol for genetic evaluation of patients with multiple colorectal adenomas and without evidence of APC gene mutation. Isr Med Assoc J. 2010;12:549-553.

Fanconi Anemia

Autosomal recessive (MIM 227650)
The most common presentation is congenital malformations, in particular a radial defect which may range from bilateral absent thumb and radii to relatively minor thumb anomalies. Other malformations such as cardiac, renal or other skeletal abnormalities are also frequent. However, in one third of the patients there are only some 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 epoxybuthane (DEB) is pathognomonic.

Molecular studies:
Fanconi anemia is heterogeneous and at least 8 complementation groups have been delineated. Among those and seven genes have been characterized

- Among Ashkenazi Jews a single mutation in the gene FAC [FAC, IVS + 4 A to T] is found. The carrier frequency was found to be 1:89 - 1:92 in screening of normal Ashkenazi Jews.
- Among Jews from Morocco, the disease is caused by mutations in FANCA. Among 13 alleles found in Moroccan Jewish patients, 2172-2173insG was found in 10 alleles (77%) and 4275delT in the other 3 (23%). The mutation [FANCA , 2172-2173insG] was found in three out of 300 normal individuals (carrier frequency 1:100).
- Among Indian Jews one mutation in FANCA, [S858R] was found in all the alleles. The mutation may be frequent in this community (2 out of 53 individuals).
- Among Jewish patients from Tunisia, a single mutation in FANCA, 890-893del, was found in all 4 alleles, but in none of 100 healthy individuals.

References:
Peleg L, Pesso R, Goldman B, Dotan K, Omer M, Friedman E, Berkenstadt M, Reznik-Wolf H, Barkai G. Bloom syndrome and Fanconi's anemia: rate and ethnic origin of mutation carriers in Isr Med Assoc J 2002; 4:95-97.
Tamary H, Bar Yam R, Shalmon L, Rachavi G, Krostichevsky, Elhasid R, Barak Y, Kaplushnik, Yaniv I, Auerbach AD, Zaizov R. Fanconi anemia group A (FANCA) mutations in Israeli non-Ashkenazi Jewish patients. Br J Haemato 2000 111:338-343.
Verlander PC, Kaporis A, Liu Q, Zhang Q, Zeligsohn U, Auerbach AD. Carrier frequency of the IVS4 + A-T mutation of the Fanconi anemia gene in the Ashkenazi Jewish population. Blood 1995; 86:4034-4038.
Whitney M A, Saito H, Jakobs PM, Gibson RA, Moses RE, Grompe MA. Common mutation in the FACC gene causes Fanconi anemia in Ashkenazi Jews. Nature Genet 1993 4: 202-205.

Fechtner syndrome (autosomal dominant Alport syndrome with leukocyte inclusions and macrothrombocytopenia)

Autosomal dominant (MIM 153640)
The disorder represents the classic Alport syndrome with hematological features and is inherited as an autosomal dominant trait.
The affected individuals present with different combinations of nephropathy, eye abnormalities, high tone sensory hearing loss, impaired liver functions, macrothrombocytopenia and polymorphonuclear inclusion bodies.

Epidemiology:
The disorder was described in a large Jewish family of Iraqi origin.

Molecular genetics:
Nonmuscle myosin heavy chain MYH9 (chromosomal locus 22q11-13)
The gene was mapped to the locus in the large Jewish family of Iraqi origin, but the mutation was not yet found.

References:
Heath KE, Campos-Barros A, Toren A, Rozenfeld-Granot G, Carlsson LE, Savige J, Denison JC, Gregory MC, White JG, Barker DF, Greinacher A, Epstein CJ, Glucksman MJ, Martignetti JA. Nonmuscle myosin heavy chain iia mutations define a spectrum of autosomal dominant macrothrombocytopenias: may-hegglin anomaly and Fechtner, Sebastian, Epstein, and Alport-like syndromes. Am J Hum Genet 2001; 69:1033-1045.
Toren A, Amariglio N, Rosenfeld-Granot G, Simon AJ, Brok-Simoni F, Pras E, Rechavi G. Genetic linkage of autosomal dominant Alport syndrome with leukocyte inclusions and macrothrombocytopenia (Fechtner syndrome) to chromosome 22q11-13. Am J Hum Genet 1999; 65:1711-1717.

Fragile X syndrome

X linked dominant (MIM 309550)
Molecular genetics:
FMR1 gene (chromosomal locus Xq27)
The disorder is caused by the absence of the FMR1 product, almost always as a result of a CGG repeat unit amplification (> 200 repeats), rarely because of a mutation in the gene.

Epidemiology:
Among the cases of fragile X syndrome in Israel published in 1997 it was apparent that the disorder is relatively frequent among Jews of Tunisian origin. In the 136 pedigrees surveyed at the time, 36 (26.4%) were of Tunisian Jewish origin (Figure). In addition, in a Tunisian Jewish control group 4 were carriers of the fragile X mutation (3 premutation, one full mutation). Studying the Tunisian Jewish chromosomes with the mutation, there was an unusually high proportion (20%) that completely devoid AGG interruption. The largest of these uninterrupted alleles was found on a unique haplotypes suggesting a founder effect that may be originating from the Island of Djerba.

In several screening programs performed among Jews in Israel the incidence of the disorder was found to be 1:3000. The carrier frequency (more 55 repeats) was approximately 1:150.

References:
Falik-Zakai TC, Shackak E, Yalon M, Borochovitz Z, Macphearson JN, Nelson DL, Eichler EE. Predisposition to the fragile X syndrome in Jews of Tunisian descent is due to the absence of AGG interruptions on a rare Mediterranean haplotype. Am J Hum Genet 1997; 60:103-112.
Geva E, Yaron Y, Shomrat R, Ben Yehuda A, Zabri S, Peretz H, Naiman T, Orr-Urtreger A. The risk for fragile X premutation expansion is lower in carriers detected by general prenatal screening than in carriers from known fragile X families. Genetic testing 2000; 4:289-292.
Pesso R, Berkenstadt, Cuckle H, Gak E, Peleg L, Frydman M, Barkai G. Screening for fragile X syndrome in women of reproductive age. Prenat Diag 2000 20:611-614.
Toledano-Alhadef H, Basel-Vagnagaite L, Magal N, Davidov B, Ehrlich S, Drasinover V, Taub E, Halpern GJ, Ginott N, Sohat M. Fragile X carrier screening and the prevalence of mutation and full mutation carriers in Israel. Am J Hum Genet 2001; 69:351-360.

Frontotemporal dementia

Autosomal dominant (MIM 600274)
Frontotemporal dementia with parkinsonism linked to chromosome 17q21-22 (FTDP-17) is an autosomal dominant tauopathy manifested by a variable combination of personality changes, cognitive decline and hypokinetic-rigid movement disorder.
In a three-generation family of Jewish-Algerian origin the family members had a fairly stereotyped clinical course with early personality changes from their late 30s followed within a period of 1-2 years by a progressive cognitive and motor deterioration eventually leading to a state of akinetic mutism or death 3-5 years after the initial symptoms. The main clinical manifestations included severe dementia and hypokinetic-rigid movement disorder associated with supranuclear gaze impairment, pyramidal signs and frontal release signs. Brain imaging disclosed a variable degree of frontotemporal atrophy, ventriculomegaly and regional cerebral hypoperfusion or glucose hypometabolism. Frontal lobe biopsy in the proband revealed weak tau immunoreactivity in a few cortical neurons, in rare neurites and in some glial cells with no neurofibrillary tangles.

Epidemiology
The disorder was described in one Agerian Jewish family

Molecular genetics
Microtubule associated protein tau gene (chromosomal locus 17q21.1)
The patients were heterozygous for the P301S mutation

References
Lossos A, Reches A, Gal A, Newman JP, Soffer D, Gomori JM, Boher M, Ekstein D, Biran I, Meiner Z, Abramsky O, Rosenmann H.Frontotemporal dementia and parkinsonism with the P301S tau gene mutation in a Jewish family. J Neurol. 2003; 250:733-740.
Werber E, Klein C, Grunfeld J, Rabey JM. Phenotypic presentation of frontotemporal dementia with Parkinsonism-chromosome 17 type P301S in a patient of Jewish-Algerian origin. Mov Disord. 2003; 18:595-598.

Galactosemia

Autosomal recessive (OMIM 230400)
Failure to thrive is the most common initial clinical symptom of galactosemia. Vomiting or diarrhea usually begins within a few days of milk ingestion. Jaundice of intrinsic liver disease may be accentuated by the severe hemolysis occurring in some patients. Cataracts have been observed within a few days of birth. These may be found only on slit-lamp examination and missed with an ophthalmoscope, since they consist of punctate lesions in the fetal lens nucleus. There appears to be a high frequency of neonatal death due to E. coli sepsis, with a fulminant course.

Epidemiology and molecular genetics
There is no known increase prevalence among Jews, but a same 5kb deletion was found in several non related families of Ashkenazi Jewish origin. the carrier frequency is 1:127 (six out 760 DNA samples)

References
Elsas LJ, Lai K. The molecular biology of galactosemia. Genet Med 1998 1:40-48.
Goldstein N, Cohen Y, Sigalov E, Vilensky B, Anikster Y. High carrier frequency of an unusual deletion mutation of the GALT gene in the Ashkenazi population [abstract 1447]. Presented at the annual meeting of The American Society of Human Genetics, October 24, 2007, San Diego, California.

Gaucher disease type I

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. Three forms of presentation of Gaucher type I are distinguished. One form is asymptomatic and the disease is discovered in an apparently healthy individual; the other form is severe with symptoms appearing in early childhood, mainly splenomegaly, anemia thrombocytopenia and often symptoms related to the bone involvement such as pains or pathological fractures. The third form is the intermediate, in which the age of onset is at the second and third decade of life and 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.
A clinical association has been reported between type 1 Gaucher disease and parkinsonism. Several data suggest that heterozygosity for a *GBA* mutation may predispose Ashkenazi Jews to Parkinson's disease.
The clinical symptoms and typical Gaucher cells in the bone marrow were the basis for the diagnosis of the disease. The biochemical diagnosis is established by the demonstration of a deficiency of glucocerebrosidase activity in white blood cells. It should be noted that in Gaucher type I patients the residual activity of the enzyme is sometimes rather high up to 20% of the mean normal control values. Heterozygotes are identified by enzymatic determinations in lymphocytes with 90% accuracy.

Epidemiology:
The disease is frequent among Ashkenazi Jews. Since the proportion of asymptomatic patients has never been clearly elucidated, the precise frequency of the disease is not known. With the knowledge of the mutations frequent among Ashkenazi Jews, studies were conducted among asymptomatic adults and the percentage of carrier frequency was found to be 6%. In a screening for the 4 mutations most frequently found in affected patients, the mutation N370S accounted for 85% of the mutations, 84GG for 6%, L444P for 3.5% and IVS2+1A for 1%. In a recent survey it seems that the mutation 1604A (R117H) which is rare among patients is relatively frequent (6.25%) and the most probable explanation is that it is a mild mutation and therefore is underrepresented among the patients.

Biochemical defect:
The deficiency of the lysosomal enzyme glucocerebrosidase is the cause of the accumulation of glucocerebroside mainly in the reticulo-endothelial system.

Molecular genetics:
Glucocerebrosidase gene (chromosomal locus 1q21)
The most frequent mutation is N370S which is always associated with the adult type of the disease and accounts for 77% of the mutated alleles in large series of affected patients. Two other relatively frequent mutations 84GG (13%) and L444P (3%) are usually associated with a more severe phenotype. The mutation IVS2+1A accounts for 2.5% of the mutated alleles in Gaucher disease patients.

References:

Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R.Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2004; 351:1972-1977.

Beutler E, Gelbart T, Kuhl W, Zimran A, West C. Mutations in Jewish patients with Gaucher disease. Blood 1992; 79:1662-1666.

DeMarchi JM, Caskey T, Richards CS. Population specific screening by mutation analysis for diseases frequent in Ashkenazi Jews. Hum Mut 1996 8:116-125.

Goker-Alpan O, Schiffmann R, LaMarca ME, Nussbaum RL, McInerney-Leo A, Sidransky E.Parkinsonism among Gaucher disease carriers. J Med Genet 2004; 41:937-940.

Horowitz M, Pasmanik-Chor M, Borochowitz Z, Falik-Zaccai T, Heldmann K, Carmi C, Parvari R, Beit-Or H, Goldman B, Peleg L, Levy-Lahad E, Renbaum P, Legum S, Shomrat R, Yeger H, Benbenisti D, Navon R, Dror V, Shohat M, Magal N, Navot N, Eyal N. Prevalence of glucocerebrosidase mutations in the Israeli Ashkenazi Jewish population. Hum Mutat 1998; 12:240-244.

Generalized epilepsy with febrile seizures plus (GEFS+)

Autosomal recessive (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 alpha1-subunit, SCN1A (chromosomal locus 2q)
A novel SCN1A mutation [V1353L] was identified in a family of Ashkenazi 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 alpha1-subunit mutations in generalized epilepsy with febrile seizures plus. Am J Hum Genet 2001; 68:859-865.

German syndrome

Autosomal recessive (MIM 231040)
In three different families newborns presenting with multiple contractions and dysmorphism were reported. All children presented with clubfeet, contracture of the knees and the fingers and hypotonia. In the family reported by Lewin and Huges the sibs presented lymphedema.

Epidemiology:
The disease has been reported in three Ashkenazi Jewish families.

Molecular genetics:
Unknown

References:
German J, Morillo-Cucci A, Simpson J, Chaganti RSK. Generalized dysmorphia of a similar type in 2 unrelated babies. Birth Defects Orig Art Ser XI(2) 34-38 1975.
Lewin SO, Hughes HE. German syndrome in sibs. Am J Med Genet 1987;26: 385-390.

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 and Molecular genetics:
cytochrome P4501B1 gene (CYP1B1).
MYOC (chromosomal locus 2p22-p21)
The disease has been diagnosed in several Jewish families in most the molecular basis is unknwon. An Ashkenazi family had mutations in the CYP1B1 gene [Arg368His, R48G, A119S, and L432V haplotypes]. An Ashkenazi-Sephardic family had a digenic inheritance: one mutation on the CYP1B1 gene [1908delA, Sephardic] with a second missense mutation on the MYOC gene [R76K, Ashkenazi]).

References:
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.

Glaucoma, juvenile open angle (JOAG)

Autosomal dominant (MIM 601652)
Open angle glaucoma is a frequent for of glaucoma. Juvenile onset glaucoma is a dominat disorder with an early age of onset between 10 and 35 years of age.

Epidemiology:
The disease has been reported in one Caucasian Jewish family.

Molecular genetics:
Myocliin MYOC (chromosomal locu 1q21-q31s)
A novel MYOC mutation [Y371D] was identified in the patients.

References:
Avisar I, Lusky M, Robinson A, Shohat M, Dubois S, Raymond V, Gaton DD.
The novel Y371D myocilin mutation causes an aggressive form of juvenile open-angle glaucoma in a Caucasian family from the Middle-East. Mol Vis. 2009 ;15:1945-1950.

Glucocorticoid deficiency, familial (FGD)

Autosomal recessive (MIM 202200)
The index patient presented at the age of 19 months with hypocortisolism, severe psychomotor retardation, myoclonic seizures, spastic quadriparesis and microcephaly. A female sibling succumbed during the neonatal period due to sepsis and adrenal crisis

Epidemiology:
The disease has been reported in one Ethiopian Jewish family.

Molecular genetics:
Melanocortin-2 receptor accessory protein MRAP (chromosomal locus 18p11.2)
A novel MRPA mutation [L31X] was identified in a family of Ethiopian origin.

References:
Modan-Moses D, Ben-Zeev B, Hoffmann C, Falik-Zaccai TC, Bental YA, Pinhas-Hamiel O, Anikster Y.Unusual presentation of familialglucocorticoid deficiency (FGD) with a novel MRAP mutation. J Clin Endocrinol Metab. 2006; 91:3713-3717.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

X linked recessive (MIM 305900)
Individuals with G6PD deficiency are generally healthy. Severe hemolysis may occur as a result of interaction with exogenous factors, mainly oxidant drugs and /or infections. Various drugs may cause hemolysis, however, they are not always associated with hemolysis after their ingestion by an individual with G6PD deficiency, and it is postulated that other factors influence the susceptibility to infection. Generally, the most common cause of hemolysis is infection. In the variant predominant in Mediterranean countries the hemolysis may be caused by fava beans. Favism may also occur in female heterozygotes but it is usually much milder.

Epidemiology:
G6PD deficiency is found in high incidence in Jews from the Middle East countries, mainly from Kurdistan, Iran and Iraq. Among Kurdish Jews more than 50% of the males are affected, 25% of the Iraqi Jews and 15% of the Iranian Jews. G6PD deficiency is also found with an increased incidence among Jews from India (Cochin) affecting some 10% of the males, 6% of the males from Lebanon-Syria, 5% of the males from Yemen, and 4% of the males from Egypt.

Biochemical defect:
G6PD is the first enzyme in the conversion of glucose-6-phosphate to the pentose-phosphate pathway. This step is essential for the generation of NADPH which functions as a hydrogen donor for various cellular reactions. Thus, the deficiency of this enzyme reduces the content of cellular NADPH, leading to the possible toxic effects of various oxidants. G6PD functions as a dimer or tetramer of identical subunits. Over 300 variants of G6PD deficiency have been recognized varying in the level of residual enzyme activity and electrophoretic mobility. The variants are classified in five groups according to the clinical severity and the level of residual enzyme activity. The residual G6PD in Mediterranean countries is known as the B variant, since it migrates in electrophoresis with the common enzyme B.

Molecular genetics:
G6PD gene (chromosomal locus Xq28)
The G6PD gene has been cloned and numerous mutations have been characterized. The most common mutation in the Mediterranean variant is a C-T transition at base position 563, substituting serine to phenylalanine.

References:
Luzzatto L, Mehta A. Glucose-6-phosphate dehydrogenase deficiency. In: The metabolic basis of inherited disease. 6th edition. Eds Scriver CR, Beaudet AL, Sly WS, Valle D. McGraw Hill Book Co NY 1989 pp 2237-2265.

Glutaric acidemia I

Autosomal recessive (MIM 231670)
Glutaricacidemia type I is a metabolic disorder characterized by progressive dystonia and athetosis due to gliosis and neuronal loss in the basal ganglia. Macrocephaly is often seen at birth. On computerized tomography the patients have unique pattern of as well as dilatation of the insular cisterns, regression of the temporal lobes, with 'bat wings' dilatation of the Sylvian fissures and hypodensity of the lenticular nuclei.

Epidemiology:
The disorder seems to be rare among Jews.

Molecular genetics:
Glutaryl-CoA dehydrogenase gene (chromosomal locus 19p13.2)
In one family of Kurdish origin the patients were homozygous for the mutation 1173delG and in one family of Iraqi origin they were homozygous for G110R.
One family of mixed origin the parent from Syria was heterozygous for S119L and the Ashkenazi Jew for M405V

References:
Amir N, El-Peleg O, Shalev RS, Christensen E.Glutaric aciduria type I: clinical heterogeneity and neuroradiologic features. Neurology 1987; 37:1654-1657.
Anikster 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.
Goodman SI, Stein DE, Schlesinger S, Christensen E, Schwartz M, Greenberg CR, Elpeleg ON. Glutaryl-CoA dehydrogenase mutations in glutaric acidemia (type I): review and report of thirty novel mutations. Hum Mutat 1998 12:141-144.
Korman SH, Jakobs C, Darmin PS, Gutman A, van der Knaap MS, Ben-Neriah Z, Dweikat I, Wexler ID, Salomons GS. Glutaric aciduria type 1: Clinical, biochemical and molecular findings in patients from Israel.Eur J Paediatr Neurol. 2006; 11:81-89

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.

Epidemiology:
The disorder is rare, it was reported in various ethnic groups at a frequency of 1/100,000 live births.
In a large survey of Ashkenazi Jews the carrier frequency of R83C was1.4%, no carriers for the Q347X mutation were found

Biochemical defect:
Deficiency of the microsomal glucose 6 phosphatase (G6Pase) activity. The deficiency may be demonstrated in liver biopsy.

Molecular genetics:
Glucose 6 phosphatase gene (chromosomal locus 17q21)
Two mutations in the G6Pase gene are prevalent among Caucasian: R83C and Q347X. Most Jewish patients of Ashkenazi origin examined had the R83C mutation. Some were found to carry Q347X.

References:
Ekstein J, Rubin BY, Anderson SL, Weinstein DA, Bach G, Abeliovich D, Webb M, Risch N. Mutation frequencies for glycogen storage disease Ia in the Ashkenazi Jewish population. Am J Med Genet. 2004;129A:162-164.
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 JY. 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 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 has been diagnosed in one Iranian Jewish family

Molecular genetics:
Acid alpha glucosidase gene GAA (chromosomal locus 17q252-q253)
In the Iranian Jewish family the mutation was [G648P]

Glycogen storage disease type III

Autosomal recessive (MIM 232400)
The clinical symptoms are related to the accumulation of glycogen in the liver and the muscular system. They often differ from patients to patients as well as in the same patient within time. The symptomatology in infancy and childhood is usually similar to GSD type I (von Gierke) - including hypoglycemic convulsions, fasting ketosis, elevated free fatty acids hyperlipemia, growth retardation and hepatomegaly. While the disease is severe in the first years of life, in some cases there is a spontaneous improvement at puberty including disappearance of hepatomegaly and normal growth. Some adults may even become clinically normal. Muscular symptoms usually appear only in adults and are found only in some of the patients. They consist of progressive muscular weakness with some wasting. Most of these patients have an abnormal ECG and EMG.

Epidemiology:
The disease has been reported with an increased incidence among Jews from North Africa, mainly from Morocco. The incidence is estimated to be 1:5,000 in this community.

Biochemical defect:
Deficiency of the debrancher enzyme amyl-1,6-glucosidase. The deficiency may be demonstrated in erythrocytes, muscle or liver.

Molecular genetics:
AGL gene (chromosomal locus 1p21)
A single mutation in the AGL gene (4455delT) was found in all 12 North African Jewish patients examined.

References:
Levin S, Moses SW, Chayot R, Jadoga N and Steinitz. Glycogen storage disease in Israel. A clinical, biochemical and genetic study. Israel J Med Sci 1967;3:397-410.
Parvari R, Moses S, Shen J, Hershkovitz E, Lerner A, Chen YT. A single base deletion in the 3' coding region of glycogen debranching enzyme is prevalent in glycogen storage disease type IIIA in a population of North African Jewish patients. Eur J Genet 1997;5:266-270.

Glycogen storage disease type IV, adult polyglucosan body disease

Autosomal recessive (MIM 263570)
The patients present with variable combinations of cognitive impairment, pyramidal tetraparesis, peripheral neuropathy and neuronogenic bladder. Less common manifestations include signs of cerebellar dysfunction, isolated dementia, extrapyramidal signs and seizures.

Epidemiology:
The disease has been reported with an increased incidence among Ashkenazi Jews. However, it is a rare disorder and the mutation was not found in a sample of 140 unrelated control Ashkenazi Jews. In a study from Canada the mutation was found with a gene frequency of 1 in 34.5 (95% CI: 0.0145-0.0512),

Biochemical defect:
Deficiency of the glycogen branching enzyme.

Molecular genetics:
GBE gene (chromosomal locus 3p12)
A single mutation in the GBE gene c.1076A>C (Tyr329Ser) was found in all Jewish patients examined.

References:
Hussain A, Armistead J, Gushulak L, Kruck C, Pind S, Triggs-Raine B, Natowicz MR The adult polyglucosan body disease mutation GBE1 c.1076A>C occurs at high frequency in persons of Ashkenazi Jewish background.. Biochem Biophys Res Commun. 2012 Sep 21;426:286-288.
.Lossos A, Meiner Z, Barash V, Soffer D, Schlesinger I, Abramsky O, Argov Z, Shpizen S, Meiner V. Adult polyglucosan body disease in Ashkenazi Jewish patients carrying the Tyr329Ser mutation in the glycogen branching enzyme gene. Ann Neurol 1998; 44:867-872

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:
The disease was reported in three unrelated families of Jews from the Caucasus region and Two unrelated Yemenite Jewish patients.

Molecular genetics:
PYGM gene glycogen myophosphorylase is localized to 11q13.
In the Jews from the Caucasian region a same mutation was characterized in two unrelated Yemenite Jewish patients a nonsense mutation was found in homozygosity [R270X]. An Ahskenazi individual mother of a patient was carrier of another mutation [R602Q]

References:
Hadjigeorgiou GM, Sadeh M, Musumeci O, Dabby R, De Girolami L, Naini A, Papadimitriou A, Shanske S, DiMauro S.Molecular genetic study of myophosphorylase deficiency (McArdle's disease) in two Yemenite-Jewish families. Neuromuscul Disord 2002;12:824-827.
Haimi Cohen Y, Shalva N, Markus-Eidlitz T, , Sadeh M, , Dabby R, Weintrob Y, Podeh-Shakked B, , Zeharia A, , Anikster Y. McArdle Disease: A novel mutation in Jewish families from the Caucasus region. Molecular Genetics and Metabolism. 2012;106:379-381.

Glycogenosis VII or phosphofructokinase deficiency (late onset)

Autosomal recessive (MIM 232800)
The typical picture of phosphofructokinase deficiency (glycogenosis VII) consists of exercise intolerance and exertional myalgia associated with laboratory evidence of chronic mild hemolysis.

Epidemiology:
Most of the patients reported are Ashkenazi Jews or Japanese. The incidence of the disorder in Ashkenazi Jews is unknown, however, in the screening of 250 healthy individuals, one person was found to carry one of the three mutations detected in the patients.

Biochemical defect:
Phosphofructokinase (PFK) catalyzes the rate-limiting step of glycolysis. There are three isozymes which are encoded by different genes. PFK-M is predominant in skeletal muscle, heart and brain and is found in these tissues as a tetramer of 4 identical subunits. Muscles are totally dependent of PFK-M to utilize glucose as an energy source while other isozymes are used in blood cells.

Molecular genetics:
PFK gene (chromosomal locus 12q13.3)
PFK deficiency in Ashkenazi Jews is caused by at least 3 different mutations [IVS5DS, G-A, +1]; [ARG39LEU], [ARG95TER] in the PFK gene. 2 mutations [IVS5DS, G-A, +1] and the frame shift mutation in exon 22 accounts for 17 of the 18 alleles causing the disease.

References:
Argov Z, Barash V, Soffer D, Sherman J, Raben N. Late onset muscular weakness in phosphofructokinase deficiency due to exon5/intron5 junction point mutation: A unique disorder or the natural course of this glycolytic disorder? Neurology 1994;44:1097-1100.
Sherman JB, Raben N, Nicastri C, Argov Z, Nakajima H, Adams EM, Eng CM, Cowan TM, Plotz PH. Common mutations in the phosphofructokinase-M gene in Ashkenazi Jewish patients with glycogenosis VII and their population frequency. Am J Hum Genet 1994;55:305-313.

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:
The disease has been diagnosed in 3 Moroccan Jewish patients in Israel (Ze1gler M).

Molecular genetics:
beta-galactosidase-1 gene GAA (chromosomal locus 3p21.33)
The Moroccan Jewish patients were homozygous for [D144G]

Growth hormone deficiency (isolated)

Autosomal recessive (MIM 262400)
Newborns are normal in length and weight. Some may have micropenis and/or fasting hypoglycemia. The growth is delayed and skeletal maturation is unusually delayed in proportion to their height retardation. Truncal obesity, facial appearance younger than expected, delayed dentition, and high pitched voice are frequent. Puberty may be delayed but fertility is normal.

Epidemiology:
The disease was reported in particular among Jews from Morocco, Iran and Iraq.

Biochemical defect:
The affected patients have isolated growth hormone deficiency.

Molecular genetics:
Growth hormone gene (chromosomal locus 17q22-24)
The Jewish patients from Iran, Iraq and Yemen have a same 7.5 kb deletion in the growth hormone gene which occurs on different haplotypes, suggesting that it is a recurrent event.

References:
Adam A, Josefsberg Z, Pertzelan A, Zadik Z, Chemke JM, Laron Z. Occurrence of four types of growth hormone related dwarfism in Israeli communities. Eur J Pediatr 1981;137:35-39.
Laron Z, Kelijman M, Pertzelan 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.

Hereditary mixed polyposis syndrome

Autosomal dominant (MIM 601228)
Hereditary mixed polyposis syndrome (HMPS) is characterized by the development of a variety of different colorectal tumors, including atypical juvenile polyps, hyperplastic polyps with areas of dysplasia (serrated adenomas), classical adenomas, and carcinoma. In contrast to familial adenomatous polyposis, the disease appears to be confined to the large bowel. Most older individuals present with colorectal carcinoma, whereas younger individuals present with polyps of either the atypical juvenile or hyperplastic type.

The phenotypes among the families are very similar, with members having developed multiple, classical colorectal adenomas and carcinomas and some have also developed early-onset tumors. Those tumors have features of both `classical' adenomas and hyperplastic polyps, referred to variously as "dysplastic hyperplastic polyps," "mixed hyperplastic/adenomatous polyps," or "serrated adenomas".

Epidemiology:
The disease has been reported in 5 Ashkenazi Jewish families.

Molecular genetics:
The disease has been mapped to 15q13–q14 in all the Ashkenazi Jewish families and a similar haplotype was found. The shared haplotype is most probably derived from a common founder. Two of the families originate from Lithuania.

References:
Jaeger EEM, Woodford-Richens KL, Lockett M, Rowan AJ, Sawyer E, Heinimann K, Rozen P, Murday VA, Whitelaw SC, Ginsberg A, Atkin WS, Lynch HT , Southey MC, Debinski H, Eng C, Bodmer WF, Talbot IC, Hodgson SV, Thomas HJW, Tomlinson I PM. An ancestral Ashkenazi haplotype at the HMPS/CRAC1 Locus on 15q13–q14 is associated with Hereditary Mixed Polyposis Syndrome. Am J Hum Genet 2003;72:1261-1267.

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:

Table 2. Seven recurrent/founder mutations among the Israeli population

Mutation	Gene	Number families	Origin
c.1906G>C; p.A636P	*MSH2*	33	Ashkenazi[a]
c.3959_3962delCAAG	*MSH6*	3	Ashkenazi
c.3984_3987dupGTCA	*MSH6*	11	Ashkenazi
c.705delA	*MSH2*	1	Druze[b]
c.2192T>G; p.L731*	*PMS2*	3	Iranian
c.1771-1772delGA	*MLH1*	3	Afghan
c.970_971del CA	*MSH2*	6	Georgian

References:
Goldberg Y, Porat RM, Kedar I, Shochat C, Sagi M, Eilat A, Mendelson S, Hamburger T, Nissan A, Hubert A, Kadouri L, Pikarski E, Lerer I, Abeliovich D, Bercovich D, Peretz T. Mutation spectrum in HNPCC in the Israeli population. Fam Cancer 2008;7: 309-317.
Goldberg Y, Porat RM, Kedar I, Shochat C, Galinsky D, Hamburger T, Hubert A, Strul H, Kariiv R, Ben-Avi L, Savion M, Pikarsky E, Abeliovich D, Bercovich D, Lerer I, Peretz T. An Ashkenazi founder mutation in the MSH6 gene leading to HNPCC. Fam Cancer 2010;9:141-150.
Goldberg Y, Barnes-Kedar I, Lerer I, Halpern N, Plesser M, Hubert A, Kadouri L, Goldshmidt H, Solar I, Strul H, Rosner G, Baris HN, Peretz T, Levi Z, Kariv R. Genetic features of Lynch syndrome in the Israeli population. Clin Genet. 2014 Nov 28.
Foulkes WD, Thiffault I, Gruber SB, Horwitz M, Hamel N, Lee C, Shia J, Markowitz A, Figer A, Friedman E, Farber D, Greenwood CM, Bonner JD, Nafa K, Walsh T, Marcus V, Tomsho L, Gebert J, Macrae FA, Gaff CL, Paillerets BB, Gregersen PK, Weitzel JN, Gordon PH, MacNamara E, King MC, Hampel H, De La Chapelle A, Boyd J, Offit K, Rennert G, Chong G, Ellis NA. The founder mutation SH2*1906G-->C is an important cause of hereditary nonpolyposis colorectal cancer in the Ashkenazi Jewish population. Am J Hum Genet. 2002;71:1395-1412.
Toledano H, Goldberg Y, Kedar-Barnes I, Baris H, Porat RM, Shochat C, Bercovich D, Pikarsky E, Lerer I, Yaniv I, Abeliovich D, Peretz T.Homozygosity of MSH2 c.1906G-->C germline mutation is associated with childhood colon cancer, astrocytoma and signs of Neurofibromatosis type I. Fam Cancer. 2009;8:187-194.

Hereditary hemochromatosis

Autosomal recessive (MIM 235200)
The clinical features of hemochromatosis include cirrhosis of the liver, diabetes, hypermelanotic pigmentation of the skin, and heart failure. Primary hepatocellular carcinoma, complicating cirrhosis, is responsible for about one-third of deaths in affected homozygotes.

Molecular genetics:
HFE gene (chromosomal locus 6p21.3)
Two mutations are frequent C282Y and H63D

Epidemiology:
The disease is relatively rare among Jews, it has been reported in three unrelated Moroccan Jewish families
H63D allele frequency Ashkenazi 11.5%, Sepharadi 12.1%, North African 13.7% and oriental 11.7%.
C282Y allele frequency Ashkenazi 1.4%, Sepharadi 0.24%, North African 1.0% and oriental 0.24%.

References:
Matas M, Guix P, Castro JA, Parera M, Ramon MM, Obrador A, PirconellA. Prevalence of HFE C282Y and H63D in Jewish populations and clinical implications of H63D homozygosity. Clin Genet 2006; 69:155-162.
Reish O, Shefer-Kaufmann N, Shimshoni DC, Renbaum P, Orr-Urtreger A, Steiner H, Rapoport M, Levy-Lahad E, Altarescu G. Frequencies of C282Y and H63D alleles in the HFE gene among various Jewish ethnic groups in Israel: a change of concept required.Genet Med 2010; 12:122-125.

Hereditary sensory autonomic neuropathy

Autosomal recessive (MIM 201300)
The disease was reported in a consanguineous Ahkenazi familyin which 4 cases were reported. The three affected children had clinical features typical for familial dysautonomia with a more severe clinical course and all had additional contractures. The 4rth case was diagnosed during pregnancy that was terminated because of bilateral club feet and hand contractures.

Molecular genetics:
DST gene (chromosomal locus 6p12.1*)*
The mutations c.14865was found in all the patients.

References
Edvardson S, Cinnamon Y, Jalas C, Shaag A, Maayan C, Axelrod FB, Elpeleg O. Hereditary sensory autonomic neuropathy caused by a mutation in dystonin. Ann Neurol. 2012 :569-572.

Hereditary spastic paraparesis, type 49

Autosomal recessive (MIM)
All affected individuals presented during the second year of life as a result of hypotonia and developmental delay. They had short stature, mild brachycephalic microcephaly, a round face, a low anterior hairline, dental crowding, a short broad neck, and a chubby appearance. The neurological phenotype included motor and cognitive delay followed by moderate to severe intellectual disability and hypotonia that, in four out of five individuals who developed independent walking, evolved until the end of the first decade of life into a spastic, rigid ataxic gait. Speech, when present, was dysarthric, their faces were hypomimic (although with a friendly disposition), and deep-tendon reflexes were absent.
All affected individuals had recurrent pulmonary infections due to gastresophageal-reflux disease. Ongoing severe central-apnea episodes were characteristic of all individuals initially during sleep and evolved with age into the wake state. Four of the individuals had recurrent episodes of decreased alertness, aggravation of hypotonia, and inefficient respiration requiring mechanical ventilation.

Epidemiology:
The syndrome has been reported in three Jewish Bukharian families. In 150 Jewish Bukharian controls 4 were carriers (2.67%)

Molecular genetics:
TECPR2 gene (chromosomal locus 14q32.31*)*
The mutation c.3416delT (p.Leu1139Argfs*75) was found in all the patients

References
Oz-Levi D, Ben-Zeev B, Ruzzo EK, Hitomi Y, Gelman A, Pelak K, Anikster Y, Reznik-Wolf H, Bar-Joseph I, Olender T, Alkelai A, Weiss M, Ben-Asher E, Ge D,. Shianna KV, Elazar Z, Goldstein DB, Pras E, Lancet D. Mutation in TECPR2 Reveals a Role for Autophagy in Hereditary Spastic Paraparesis. Am J Hum Genet 2012;91:1065-1072

Hereditary spastic paraparesis, type 11

Autosomal recessive (MIM 604360)
The 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 an Ahkenazi family.

Molecular genetics:
SPG11gene (chromosomal locus 15q13-q15)
The mutations c.4307_4308 delCTGT and c.5986_5987insT were found in a patient.

References
Stevanin G, Azzedine H, Denora P, Boukhris A, Tazir M, Lossos A, Rosa AL, Lerer I, Hamri A, Alegria P, Loureiro J, Tada M, Hannequin D, Anheim M, Goizet C, Gonzalez-Martinez V, Le Ber I, Forlani S, Iwabuchi K, Meiner V, Uyanik G, Erichsen AK, Feki I, Pasquier F, Belarbi S, Cruz VT, Depienne C, Truchetto J, Garrigues G, Tallaksen C, Tranchant C, Nishizawa M, Vale J, Coutinho P, Santorelli FM, Mhiri C, Brice A, Durr A; on behalf of the SPATAX consortium. Mutations in SPG11 are frequent in autosomal recessive spastic paraplegia with thin corpus callosum, cognitive decline and lower motor neuron degeneration. Brain. 2007; 131:772-784.

Hermansky-Pudlak syndrome

Autosomal recessive (MIM 203300)
Hermansky-Pudlak syndrome is a disorder of the formation of intracellular vesicles. Patients exhibit various degrees of occulocutaneous 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. Some patients develop granulomatous colitis and fatal pulmonary fibrosis.
The diagnosis is based on the absence of dense granules in platelets in EM.

Epidemiology:
The disease has been reported in several Ashkenazi Jewish patients with in rule a mild form of the disorder.

Molecular genetics:
HPS3 gene (chromosomal locus 3q24)
Three different genes have been involved up to now in the pathogenesis of the disease. A unique HPS3 mutation has been found among the Ashkenazi Jewish patients with an increased frequency [1303+1G→A] (detected in one out of 235 random DNA samples).

References:
Huizing M, Anikser Y, Fitzpatrick DL, Jeong AB, D'Souza M, Raushe M, Toro JR, Kaiser-Kufpfer MI, White JG, Gahl WA. Hermansky-Pudlak syndrome type 3 in Ashkenazi Jews and other non-Puerto-Rican patients with hypopigmentation and platlet storage pool deficiency. Am J Hum Genet 2001; 69:1022-1032.

Hoyeraall-Hreidarsson syndrome - Dyskeratosis congenita

Autosomal recessive (MIM 300240)
Hoyeraal-Hreidarsson syndrome is similar to autosomal recessive dyskeratosis congenita-5 characterized by onset of bone marrow failure and immunodeficiency in early childhood. Most patients also have growth and developmental delay and cerebellar hypoplasia.

Molecular genetics and epidemiology:
RTEL1 gene (chromosomal locus 20q13.33)
In two Ashkenazi Jewish families the patients were homozygous for a founder mutation R1264H (c.3791G>A). In another Ashkenazi Jewish family the patients were compound heterozygote for c.C2920T and c.G1476T. The frequency of the R1264H mutation was deternimed in a large sample of AJ from the ultraorthodox community (carrier frequency 1%) and general AJ population (carrier frequency 0.45%) while the two other mutations were not found in the random samples

TERT gene (chromosomal locus 5p15.33)
In a consanguineous Iranian Jewish family a female patient was homozygous for p.Arg901Trp (R901W).
In a family of Iraqi Jewish origin clinical features compatible with a dominant form of the disease all the affected males presented with isolated thrombocytopenia that was followed by decreased RBC and/or WBC counts. Anticipation for aplastic anemia, premature greying of hair, pulmonary fibrosis and hepatic fibrosis was observed. In 2 patients, cardiac abnormalities were detected: cardiac and cardiomegaly. Death was due to respiratory failure or hepatic failure; one patient died as a result of myocardial infarction.While all 6 males in the family were severely affected, neither of the 2 females showed overt clinical manifestations of the disease except for premature grey hair in both and borderline RBC count in one of them. A novel heterozygous missense mutation (c.1892 G>A; p.Arg631Gln), was detected in all the patients

References:
Basel-Vanagaite L, Dokal I, Tamary H, Avigdor A, Garty BZ, Volkov A, Vulliamy T.Expanding the clinical phenotype of autosomal dominant dyskeratosis congenita caused by TERT mutations. Haematologica. 2008 May 6 [Epub ahead of print]
Ballew BJ et al. A Recessive Founder Mutation in Regulator of Telomere Elongation Helicase 1, RTEL1, Underlies Severe Immunodeficiency and Features of Hoyeraal Hreidarsson Syndrome. PLoS Genet. 2013;9
Deng Z, Glousker G, Molczan A, Fox AJ, Lamm N, Dheekollu J, Weizman OE, Schertzer M, Wang Z, Vladimirova O, Schug J, Aker M, Londoסo-Vallejo A, Carrier Fedick AM, Shi L, Jalas C, Treff NR, Ekstein J, Kornreich R, Edelmann L, Mehta L, Savage SA. Screening of RTEL1 Mutations in the Ashkenazi Jewish Population. Clin Genet. 2014 Jul 22.
Kaestner KH, Lieberman PM, Tzfati Y.Inherited mutations in the helicase RTEL1 cause telomere dysfunction and Hoyeraal-Hreidarsson syndrome. Proc Natl Acad Sci U S A. 2013;1103408-16.
Marrone A, Walne A, Tamary H, Masunari Y, Kirwan M, Beswick R, Vulliamy T, Dokal I. Telomerase reverse-transcriptase homozygous mutations in autosomal recessive dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome. Blood. 2007;110:4198-4205.

HTLV-I infection susceptibility

A high prevalence of human T-lymphotropic virus type I (HTLV-I) infection among Israeli Jews originating from Mashhad (Iran) (infection rate of 60/306 20%).

References:

Miller M, Achiron A, Shaklai M, Stark P, Maayan S, Hannig H, Hunsmann G, Bodemer W, Shohat B. Ethnic cluster of HTLV-I infection in Israel among the Mashhadi Jewish population. J Med Virol 1998; 56:269-274.

Hunter syndrome

X linked recessive (MIM 309900)
Hunter syndrome (mucopolysaccharidosis II) is a lysosomal storage disorder characterized by the accumulation of dermatan and heparan sulfate. Two clinical subtypes of the disease are delineated. In the severe form the child is mentally retarded and there is a progressive mental regression; in the "mild" form the intellect remains intact. In both subtypes of the disease the accumulation of mucopolysaccharides leads to skeletal deformities including typical facial changes, short stature, severe joint limitation and severe bone changes which may be seen on radiologic examination as dysostosis multiplex. The patients develop progressive respiratory and cardiac problems which lead to early death. While all the patients with the severe form die in the first or second decade; most of the patients with the mild form have a longer survival, a few of them reach adulthood.

Epidemiology:
The disease was found with an increased frequency among Jews in Israel primarily as a result of a 2-3 fold increase in the incidence among the Ashkenazi Jews as compared to the incidence of the disease in Western Europe and North America.

Biochemical defect:
Deficiency of the lysosomal enzyme iduronate sulfate sulfatase (IDS). The diagnosis is made by determination of the enzyme activity in serum or and leukocytes. Determination of IDS activity in serum allows identifying more than 90% of the carriers.

Molecular studies:
IDS gene (chromosomal locus Xq28)
Among Ashkenazi Jews different mutations were found: one C1244-1305del is recurrent and was also found in other populations.

References:
Ben Simon-Schiff E, Bach G, Hopwood JJ, Abeliovich D. Mutation analysis of Jewish Hunter patients in Israel. Hum Mutat 1994; 4:263-270.
Schaap T and Bach G. The incidence of mucopolysaccharidoses in Israel: is Hunter syndrome a "Jewish disease"? Hum Genet 1980;56:221-223.

Huntington disease

Autosomal dominant (MIM 143100)

The classic signs of Huntington disease are progressive chorea, rigidity, and dementia, frequently associated with seizures. A characteristic atrophy of the caudate nucleus is seen radiographically. Typically, there is a prodromal phase of mild psychotic and behavioral symptoms which precedes frank chorea by up to 10 years.

Epidemiology and molecular genetics:
Hungtintin gene (chromosomal locus 4p16.3)
The disease is associated with increases in the length of a CAG triplet repeat. The disorder was found with a high prevalence among Caucasian Jews and among the Karaites (Fried K).

References:
Herishanu YO, Parvari R, Pollack Y, Shelef I, Marom B, Martino T, Cannella M, Squitieri F. Huntington disease in subjects from an Israeli Karaite community carrying alleles of intermediate and expanded CAG repeats in the HTT gene: Huntington disease or phenocopy? J Neurol Sci 2009;277:143-146.
Melamed O, Behar DM, Bram C, Magal N, Pras E, Reznik-Wolf H, Borochowitz ZU, Davidov B, Mor-Cohen R, Baris HN.Founder mutation for Huntington disease in Caucasus Jews. Clin Genet. 2014 Jan 9

Hypercholesterolemia, familial

Autosomal dominant (MIM 143890)
In the heterozygotes, hypercholesterolemia is the earliest manifestation, and is often present at birth. The patients are usually asymptomatic till the second decade when arcus cornea and tendon xanthomas appear and by the end of the third decade are present in half of the heterozygotes. The principal health problem is an early appearance of coronary heart disease, usually in the fourth decade of life.
In the homozygotes the clinical picture is much more severe than in the heterozygotes. Marked hypercholesterolemia is present at birth; cutaneous xanthomas are frequent at birth and in all cases are present in the first years of life together with arcus cornea and tendon xanthomas. Homozygotes develop symptoms of atherosclerosis in childhood. Death occurs before the age of 30 from myocardial infarction in non treated patients.

Epidemiology:
The disorder was found with a much higher prevalence among South African Jews (1:67) than in the general population (1:500). The South African Jewish community originated from East Europe mainly Lithuania and settled in South Africa after the massive emigration at the end of the 19th century. It seems that most affected individuals have the same mutation and therefore most probably originated from a common ancestor.

Biochemical defect:
Elevation of cholesterol bound to low density lipoprotein.

Molecular genetics:
LDL receptor gene (chromosomal locus 19p13.2)
A similar mutation in the LDL gene was demonstrated in most Jews originating from Lithuania in South Africa and in Israel. The mutation is a 3 base pairs deletion in exon 4 of the gene; it leads to the elimination of a single amino acid (Glycine 197) from the highly conserved binding domain of the LDL receptor. The mutation is designated FH-Piscataway and is classified as a type II mutation (impaired transport and processing). It probably leads to an improper folded binding domain of the LDL receptor, and a block in transport of receptor precursor molecules to the cell surface. Therefore, extremely low expression of functional receptors encoded by this mutation is expected.

References:
Meiner V, Landsberger D, Berkman N, Reshef A, Segal P, Seftel HC, van der Westhuyzen DR, Jeenah MS, Coetzee GA, Leitersdorf E. A common mutation causing familial hypercholesterolemia in Ashkenazi Jews. Am J Hum Genet 1991; 49:443-449.
Seftel HC, Baker SG, Jenkins T, Mendelsohn D. Prevalence of familial hypercholesterolemia in Johannesburg Jews. Am J Med Genet 1989;34:545-547.

Hyperoxaluria, type III

Autosomal recessive (MIM 613616)
The patients present in general with nephrolithiasis from infancy. The clinical manifestations were hematuria, pain and or urinary tract infection. In many cases no therapy is necessary and these patients preserve their renal function and there is no recurrence of stone formation after 6 year of age.

Epidemiology and molecular genetics:
DHDPSL *gene (chromosomal locus 10q24.2)*
A similar mutation c.944_946delAGG (p. Glu315Del) was found in all the patients in 4 Ashkenazi families, in the 5th family, the patients were compound heterozygous for the same mutation and c.860G>T (p.Gly287Val)

References:
Belostotsky R, Seboun E, Idelson GH, Milliner DS, Becker-Cohen R, Rinat C, Monico CG, Feinstein S, Ben-Shalom E, Magen D, Weissman I, Charon C, Frishberg Y. Mutations in DHDPSL Are Responsible For Primary Hyperoxaluria Type III. Am J Hum Genet. 2010;87:392-329.

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 disease was reported in a Jewish family**.**

Molecular genetics:
ALPL gene (chromosomal locus 1p36.1-p34)
The patient was compound heterozygous [E274K]/ [G309R]

References
Litmanovitz, Reish O, Dolfin T, Arnon S, Regev R, Grinshpan G, Yamazaki M, Ozono K.Glu274Lys/Gly309Arg mutation of the tissue-nonspecific alkaline phosphatase gene in neonatal hypophosphatasia associated with convulsions. J Inherit Metab Dis. 2002; 25:35-40.

Idiopathic torsion dystonia (ITD)

Autosomal dominant (MIM 128100)
Dystonia is by definition a defective control of muscle tone. In torsion dystonia the muscle tone is increased leading to involuntary twisting movement or postures. Among the Ashkenazi Jews affected with ITD the onset is relatively early before the age of 20 years, the limbs are involved earlier and more severely than the axial musculature. Clinical deterioration is usually rapid at the early stages of the disease but the symptoms tend to stabilize later on. The degree of involvement varies from patient to patient. Some may suffer of generalized dystonia, in particular the younger patients, and in others the dystonia may be segmental or focal. It may be demonstrated that the disease is usually less severe and the onset is delayed among the relatives of the probands, indicating the variability of ITD and that there is a selection for diagnosis of the severely affected patients.
For many years following the work of Elridge, it was considered that ITD among Ashkenazi Jews is inherited as an autosomal recessive trait, as opposed to the classical disease which is autosomal dominant. However, more recent analysis of the data among Ashkenazi Jews indicated a similar mode of inheritance in this ethnic group as in non Ashkenazi and non Jewish patients. The differences are in the clinical presentation as well as penetrance. The penetrance of ITD is estimated to be 0.75 in non Jews and 0.3 in Ashkenazi Jews.

Epidemiology:
The disease has been reported with an increased incidence among Ashkenazi Jews; The estimated gene frequency in this group is 1/2,000 to 1/6,000.

Molecular genetics:
DYT1 gene (chromosomal locus 9q32-34*)*
A unique 3bp GAG deletion in the gene DYT1 is found in nearly all cases of the disorder in Jews and non Jews. The majority of early onset ITD cases among the Ashkenazi Jews have a similar haplotype and therefore it was estimated that the mutation first appeared approximately 350 years ago.

References:
Risch N, de Leon D, Ozelius L, Kramer P, Almasy L, Singer B, Fahn S, Breakefield X, Breesman S. Genetic analysis of idiopathic torsion dystonia in Ashkenazi Jews and their recent descent from a small founder population. Nature Genet 1995:9:152-159.
Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, deLeon D, Brin MF, Raymond D, Corey DP, Fahn S, Risch NJ, Buckler AJ, Guesella JF, Breakefield XO. The early onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nature Genet 1997;17:40-48.
Zilber N, Korczyn A D, Kahana E, Fried K,Alter M. Inheritance of idiopathic torsion dystonia among Jews. J Med Genet 1984;21:13-20.

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 reported in two Ashkenazi Jewish families.

Molecular genetics:
ABCA12 gene (chromosomal locus 2q34)
One patient was compound heterozygous [Y377X/Q2161X], the other homozygous [Q354X]

References:
Kelsell DP, Norgett EE, Unsworth H, Teh MT, Cullup T, Mein CA, Dopping-Hepenstal PJ, Dale BA, Tadini G, Fleckman P, Stephens KG, Sybert VP, Mallory SB, North BV, Witt DR, Sprecher E, Taylor AE, Ilchyshyn A, Kennedy CT, Goodyear H, Moss C, Paige D, Harper JI, Young BD, Leigh IM, Eady RA, O'Toole EA. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet. 2005;76:794-803.

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 symtpoms including two older adults (ages 50 and 68 years).

Epidemiology:
The disease has been reported in Middle Eastern Jews and Karaites, as the result of a founder mutation, with incomplete penetrance.Among the Iranian Jews the disease is frequent (1/1500).

Molecular genetics:
UDP-Nacetylglucosamine 2-epimerase/N-acelylmannosamine kinase gene (GNE) (chromosomal locus 9p12-13)
All the Iranian Jewish patients are homozygotes for the same missense mutation [M712T] that was found in 5 out of 73 unrelated healthy Iranian Jews.

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, Shmilevich 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-acelylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy. Nature Genet 2001; 29:83-87.

Infantile cerebral and cerebellar atrophy

Autosomal recessive (MIM 603810)
The affected children are born with normal head circumference and at 4-9 weeks of age swallowing difficulaties leading to failure to thrive, jitterness poor visual fixation and lack of traking with seizures. On examination the muscle tone is increased with clonus and exaggerated deep tendons reflexes. Later on there is no acquisition of developmental milestones and the patients suffered from marked spasticity profound retardation and occasional seizures and progressive microcephaly

Epidemiology:
The disease has been reported in Caucasian Jews, as the result of a founder mutation that was found in 4 out of 79 unrelated healthy Caucasian Jews.

Molecular genetics:
MED17 gene (chromosomal locus 11)
All the Caucasian Jewish patients are homozygotes for the same mutation [p.L371P]

References:
Kaufmann R, Straussberg R, Mandel H, Fattal-Valevski A, Ben-Zeev B, Naamati A, Shaag A, Zenvirt S, Konen O, Mimouni-Bloch A, Dobyns WB, Edvardson S, Pines O, Elpeleg O. Infantile Cerebral and Cerebellar Atrophy Is Associated with a Mutation in the MED17 Subunit of the Transcription Preinitiation Mediator Complex. AJHG 2010;87:667-6 70.

Joubert syndrome 2 (JBTS2)

Autosomal recessive (OMIM 213300)
Joubert syndrome is characterized by mihindbrain malformation, hypotonia, carebellar ataxia and developmental delay. Occulomototor 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 midely to severly 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 heterogenic group with at least 10 loci

TMEM21 (chromosomal locus 11p12-p13/3)
A mutation [R73Lc.35G>T which is predicted to result in the substitution of arginine at codon 12 by leucine (R12L) was found in all Jewish Ashkenazi patients. In a survey of 2766 anonymous Ashkenazi Jewsih samples the carrier frequency was 1:92.

References
Edvarson S, Shaag A, Zenvirt S, Erlich Y, Hannon GJ, Gomori JM, Ekstein J, Elpeleg O. Joubert syndrome 2 (JBTS2) in Ashkenazi Jews is associated with a TMEM216 mutation. Amer J Hum Genet 2010;86:1-5.
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, Sougnez 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.

Kindler syndrome

Autosomal recessive (OMIM 173650)
Kindler syndrome is a rare autosomal recessive muco-cutaneous disorder. The cutaneous features consist of trauma-induced skin blistering, particularly of acral sites, skin atrophy, poikiloderma (a combination of skin atrophy, hypo- and hyper-pigmentation and telangiectases) and varying degrees of photosensitivity . The extra-cutaneous features include colonic inflammation, gingivitis, periodontitis and mucosal inflammation affecting the oesophagus, urethra, vagina and anus. There is also an increased risk of muco-cutaneous cancer

Molecular genetics and epidemiology
FERMT1 gene (chromosomal locu 20p13s)
Hacham-Zadeh and Garfunkel described 2 related Kurdish Jewish sibships, each with first-cousin parents; 1 was affected in the first sibship and 3 were affected in the second. The proposita had had bullae on pressure areas from birth. These healed with atrophic scars. She also had severe photosensitivity on exposed areas and developed widespread poikiloderma. Bullae did not occur after age 17 years. Oral examination showed limitation of mouth opening, ankyloglossia, dental overbite, and atrophy of buccal mucosa with white spots.In one of those families an affected female was homozygous for pTyr403X who died from a muco-cutaneous squamous cell carcinoma (SCC).

References.
Hacham-Zadeh S, Garfunkel AA. Kindler syndrome in two related Kurdish families. Am J Med Genet. 1985;20:43-48.
Techanukul T, Sethuraman G, Zlotogorski A, Horev L, Macarov M, Trainer A, Fong K, Lens M, Medenica L, Ramesh V, McGrath JA, Lai-Cheong JE. Novel and Recurrent FERMT1 Gene Mutations in Kindler Syndrome. Acta Derm Venereol. 2011; 91:267-270.

Laron syndrome (Pituitary dwarfism II)

Autosomal recessive (OMIM 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 Jews from Iran (7 families), Iraq (6 families), Afganistan (2 families) Yemen (2 families) and Morocco (1 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)
A nonsense mutation in exon 2 [W15X] was found in three Jewish-Iraqi patients and a mutation in exon 7 [R211H].
Among the Iran Jewish families several mutations were found [230delT], [exon5 del]
A deletion of exon 5-6 was found among Iraqi, Iranian and Afghani Jews.
The mutations were not characterized in 5 Iranian and one Iraqi Jewish pedigrees.
In the Yemente Jewish families the patients were homozygous for R271X

References
Laron Z. Laron syndrome: the personal experience 1958-2003. J Clin Endocrinol Metab 2004; 89:1031-1044.
Laron Z, Kelijman M, Pertzelan 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.

Epidemiology:
The disorder seems to be frequent among Jews from North Africa

Molecular genetics:
Leber congenital amaurosis is a heterogeneous disorder and at least 5 loci for causative mutations have been demonstrated.
RPE65 gene (chromosomal locus 1p31)
A founder mutation c.95-2A>T (IVS2-2A>T) was found to be a prevalent cause of the disease among North African Jews (Morocco, Tunisia and Algeria). In 179 random, origin mached controls, 2 carriers were decteted (1.1% carrier frequency)
AIPL1 gene (chromosomal locus 17p13.1)
In four North African Jewish families (Libya and Morocco) the mutation p.Val71Phe was characterized.
GUCY2D gene (chromosomal locus 17p13.1)
The mutation c.389delC was reported in several families from North Africa (Morocco, Tunis and Lybia). Another mutation [620DelC] was reported in one family from Morocco.
LCA5 gene (chromosomal locus 6q14.1)
The mutation c.835C>T (p.Q296) was reported in several Ashkenazi Jewish families with a 1% carrier frequency in a sample of 96 controls

References:
Banin E, Bandah-Rosenfeld D, Obolensky A, Cideciyan AV, Aleman TS, Marks-Ohana D, Sela M, Boye SL, Sumaroka A, Roman AJ, Schwartz SB, Hauswirth W, Jacobson SG, Hemo I, Sharon D. Molecular Anthropology meets Genetic Medicine to Treat Blindness in the North African Jewish Population: Human Gene Therapy Initiated in Israel. Hum Gene Ther. 2010;21:1749-1457. Epub 2010 Nov 3. Chiang PW, Spector J, Picker E, Chung WK Founder effect of LCA5 p.Q279X mutation in the Ashkenazi Jewish population. ASHG congress 2010
Perrault I, Rozet JM, Gerber S, Ghazi I, Ducroq D, Souied E, Leowski C, Bonnemaison M, Dufier JL, Munnich A, Kaplan J. Spectrum of retGC1 mutations in Leber's congenital amaurosis. Eur J Hum Genet 2000;8:578-582.

Leigh syndrome

Autosomal recessive (OMIM 256000)
Leigh syndrome or subacute necrotizing encephalomyelopathy, is a devastating, paediatric neurodegenerative disorder characterized by bilateral, symmetric lesions in the brainstem, midbrain, pons, thalamus, basal ganglia, and cerebellum. Individuals with Leigh syndrome present with variable clinical symptoms that include hypotonia, psychomotor retardation or regression, respiratory difficulties, recurrent vomiting, nystagmus, ataxia, peripheral neuropathy, external ophthalmoplegia, loss of vision, impaired hearing, and seizures Leigh syndrome is associated with progressive neurological dysfunction and is usually lethal within the first two years of life. Biochemically, Leigh syndrome can result from a number of inherited defects in mitochondrial energy metabolism.

Epidemiology and Molecular genetics:
Leigh syndrome is a heterogeneous disorder and genetically, can be autosomal recessive, X linked, or maternally inherited, and can result from mutations in genes encoding subunits of the pyruvate dehydrogenase complex (PDHC) or subunits
of respiratory chain complexes I, II, III, IV or V, but predominantly of complexes I and IV
NDUFS4 (OMIM 602694) (chromosomal locus 2q33).
In an Ashkenazi Jewish family with three affected children harboured a homozygous [c.462delA] mutation that was found in frequency of 1:1000 in 5000 random AJ samples. In a family of Ashkenazi/sepharadi origin a compound heterozygous for [c.462delA] and [p.Lys154fs] was reported.
C20ORF7 (OMIM 612360) (chromosomal locus 20p12.1).
In 2 Ashkenazi Jewish families with affected children a homozygous [c.749G>T] mutation was found in a frequency of 1:290 in 869 random AJ samples.

References:
Anderson SL, Chung WK, Frezzo J, Papp JC, Ekstein J, DiMauro S, Rubin DY. A novel mutation in NDUFS4 cases Leigh syndrome in an Ashkenazi Jewish family. J Inherit Metab Dis. 2008;31 Suppl 2:S461-467.
Leshinsky-Silver E, Lebre A-S, Minai L, Saada A, Steffann J, Cohen St, Rötig A, Munnich A, Lev D, Lerman-Sagie T. NDUFS4 Mutations Cause Leigh Syndrome with Predominant Brainstem Involvement. Mol Genet Metab. 2009;97:185-189.
Saada A, Edvardson S, Shaag A, Chung WK, Segel R, Miller C, Jalas C, Elpeleg O. Combined OXPHOS complex I and IV defect, due to mutated complex I assembly factor C20ORF7. J Inherit Metab Dis. 2012;35:125-131

Limb girdle muscular dystrophy LGMD2

Autosomal recessive (MIM 253601)
Muscular weakness usually appears in the second half of the third decade as gait difficulties.

Epidemiology:
The disease has been reported to occur with a high frequency in Libyan Jews and among Jews of the Caucasus (Mountain Jews). A large family of Yemenite Jews has been also reported.

Molecular genetics:
Dysferlin (chromosomal locus 2p13)
All the patients from Libya are homozygotes for a single guanine deletion in a run of 4 guanines which is predicted to produce a frameshift introducing a premature stop codon downstream.
All the patients from the Caucasus were homozygous for a frameshift mutation of G deletion at codon 927 (2779delG).
In the Yemenite Jewish family a frame shift mutation at nucleotide 5711 of dysferlin was found in homozygosity.

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.
Leshinsky-Silver E, Argov Z, Rozenboim L, Cohen S, Tzofi Z, Cohen Y, Wirguin Y, Dabby R, Lev D, Sadeh M. Dysferlinopathy in the Jews of the Caucasus: A frequent mutation in the dysferlin gene. Neuromuscul Disord. 2007; 17:950-954. Epub 2007 Sep 6.
McNally EM, Ly CT, Rosenmann H, Mitrani Rosenbaum S, Jiang W, Anderson LVB, Soffer D, Argov Z. Splicing mutation in dysferlin produces limb girdle muscular dystrophy with inflammation. Am J Med Genet 2000; 91:305-312.

Lipoamide dehydrogenase deficiency

Autosomal recessive (MIM 238331)
The disease is characterized by recurrent attacks of vomiting, abdominal pain and encephalopathy with abnormal liver function. The age of onset is variable and the patients who presented in the neonatal period suffered thereafter of neurological damage while those who presented in childhood suffered from exertional fatigue between the episodes but were otherwise asymptomatic.
The LAD activity is reduced in muscle and lymphocytes in all patients.

Epidemiology:
The disease has been diagnosed in several Ashkenazi families and the carrier rate of the major mutation G229C was 1:94 among 845 random Jewish individuals.

Molecular genetics:
LAD gene (chromosomal locus 7q31-q32)
Two mutations in the LAD gene have been found among Ashkenazi patients. The [G229C] mutation is the most frequent while the [Y35X] is rare. The patients with the most severe clinical picture homozygotes were while those with later onset were compound heterozygotes for the [G229C] mutation. An additional mutation [147T] was described in one Ashkenazi family.

References:
Cameron JM, Levandovskiy V, Mackay N, Raiman J, Renaud DL, Clarke JT, Feigenbaum A, Elpeleg O, Robinson BH.Novel mutations in dihydrolipoamide dehydrogenase deficiency in two cousins with borderline-normal PDH complex activity. Am J Med Genet A. 2006;140:1542-1552.
Shaag A, Saada A, Berger I, Mandel H, Joseph A, Feigenbaum A, Elpeleg ON: Molecular basis of lipoamide dehydrogenase deficiency in Ashkenazi Jews. Am J Med Genet 1999;82:177-182.

Maturity onset diabetes mellitus, MODY

Autosomal dominant (MIM 606391)
Maturity-onset diabetes of the young is a distinct type of NIDDM with clear autosomal dominant inheritance and onset at age less than 25 years. MODY pedigrees are usually multigenerational families with penetrance of 80 to 95%. Patients have a nonobese body habitus and the so-called metabolic syndrome characterized by diabetes, insulin resistance, hypertension, and hypertriglyceridemia is absent.

Molecular genetics:
MODY1; hepatocyte nuclear factor-4-alpha gene (HNF4A) (chromosomal locus 20).

MODY2; glucokinase gene (GCK; 138079) (chromosomal locus 7).
Four Jewish families were reported one family with [Met202Thr], two families [Thr206Pro], one family with [Cyst213Arg] and the other [Thr228Met]

MODY3; hepatic transcription factor-1 gene (TCF1) (chromosomal locus 12q24.2).
In six families mutations in the gene werte reported: [Arg131Gln] (Ashkenazi), [Arg159Trp] (Ashkenazi), [Arg159Trp] (Ashkenazi), [Arg271Gln] (Ashkenazi), and [Ala174del11], [P447I] and [Prf291fsinsC].

MODY4; insulin promoter factor-1 gene (chromosomal locus 13q12.1).
MODY5; hepatic transcription factor-2 (chromosomal locus 17cen-q21.3).
MODY6; NEUROD1 gene (chromosomal locus 2q32).
MODY7; KLF11 gene (chromosomal locus 2p25).
MODY8; CEL gene (chromosomal locus 9q34).
MODY9; PAX4 gene (chromosomal locus 7q32)

References:
Stern E, Strihan C, Potievsky O, Nimri R, Shalitin S, Cohen O, Shehadeh N, Weintrob N, Phillip M, Gat-Yablonski G. Four novel mutations, including the first gross deletion in TCF1, identified in HNF-4alpha, GCK and TCF1 in patients with MODY in Israel. J Pediatr Endocrinol Metab 2007;20:909-921.

Machado-Joseph disease (spinocerebellar ataxia type 3; SCA3)

Autosomal dominant (MIM 109150)
Machado Joseph disease is a multisytem degeneration in which spinocerebellar, pyramidal, lower motor neuron, peripheral nerve, basal ganglia, extra-ocular-movement and autonomic function are impaired. The age of onset, the severity of the symptoms and the duration of the disease vary from patient to patient with some correlation to the size of the CAG expansion.
Several homozygotes have been reported among the Yemenite Jews because of the late onset of the disease and the high degree of consanguinity. In general the homozygotes were more severely affected than the heterozygotes for the same degree of expansion.

Epidemiology:
The disease has been diagnosed in several unrelated families of Jewish Yemenite origin.

Molecular genetics:
SCA3 (chromosomal locus 14q24.3-q31)
The gene includes a region of unstable CAG repeats. All the patients of Yemenite origin have the same haplotype.

References:
Lerer I, Merims D, Abeliovich D, Zlotogora J, Gadoth N. Machado Joseph disease: correlation between the clinical features, the CAG repeat length and homozygosity for the mutation. Eur J Hum Genet 1996;4:3-7.

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. The keto acids of leucine, isoleucine and valine are present in the urine, suggesting a block in oxidative decarboxylation. The keto acid of isoleucine (alpha-keto-beta-methylvaleric acid) is responsible for the characteristic odor. Five clinical phenotypes have been described which differs by their presentation and severity. The most severe is the classical, manifesting in the newborn period and results in severe neurologic manifestations, if not treated may lead to death. Less common are late onset and intermediate types of the disease.
MSUD with a defect in the E1-alpha subunit of branched-chain keto acid dehydrogenase is referred to as type IA; the type with a defect in the E1-beta subunit (248611) is referred to as type IB; the type with a defect in the E2 subunit (248610) is referred to as type II; and the type with a defect in the E3 subunit is referred to as type III. The E3-deficient MSUD presents a combined deficiency of branched-chain alpha-keto acid dehydrogenase, pyruvate dehydrogenase, and alpha-keto glutarate dehydrogenase complexes. This is the result of E3 being a common component of the 3 mitochondrial multienzymes.

Epidemiology:
The classical form disease has been diagnosed in several Ashkenazi Jewish patients in the newborn screening in New York. In a random sample of 1014 AJ individuals from New York the carrier frequency of [R183P] was 1:113.

Molecular genetics:
BCKDHB gene (chromosomal locus 6p22.p21)
In several patients the [R183P] mutation was characterized in homozygosity. The mutation affects the E1b subunit in the decarboxylase (E1) component of the branched-chain a-ketoacid dehydrogenase complex.
Among single AJ patients other mutations were characterized: [E2ΔAT], [E442X], [G278S].

References:
Edelmann L, Wasserstein MP, Kornreich R, Sansaricq C, Snyderman SE, Diaz G. Maple Syrup Urine Disease: identification and carrier frequency determination of a novel founder mutation in the Ashkenazi Jewish population. Am J Hum Genet 2001; 69:863-868.

Megalencephalic leukoencephalopathy (vacuolating)

Autosomal recessive (MIM 605908)
Vacuolating megalencephalic leukoencephalopathy is characterized by accelerated head growth beginning in the first year of life. Subsequently the affected children develop neurologic involvement. During the first year of life the children are macrocephalic with a relatively benign motor disability or clumsiness evolving into ataxia and spasticity with no significant cognitive deterioration. Most develop a seizure disorder and a severe cerebral white matter change on neuroimaging. The progression is very slow and the cognitive functions remain almost intact.

Epidemiology:
The disease has been found to be relatively frequent among Jews originating from Libya. Screening of 200 normal Libyan Jewish individuals for the.G59E mutation, revealed a carrier rate of 1:40.

Molecular genetics:
MLC1 gene (chromosomal locus 22qtel)
One unique mutation [G59E] was found in all the Jewish patients in Israel from Libya and Turkey.

References:
Ben-Zeev B, Gross V, Kushnir T, Shalev R, Hoffman C, Shinar Y, Pras E, Brand N. Vacuolating megalencephalic leukoencephalopathy in 12 Israeli patients. J Child Neurol 2001;16:93-99.
Ben-Zeev B, Levy-Nissenbaum E Lahat H, Anikster Y, Shinar Y, Brand N, Gross-Tzur V, MacGregor D, Sidi R, Kleta R, Frydman M, Pras E. Megalencephalic Leukoencephalopathy with Subcorical Cysts; a Founder Effect in Israeli Patients and a Higher than expected Carrier Rate Among Libyan Jews. Hum Genet Hum Genet. 2002;111:214-218.

Melanoma cutaneous, malignant

Autosomal dominant (MIM 155600)
About 10% of melanoma patients come from families with another affected individual. The majority of families with predisposition to melanoma have a germline mutation impinging p16.

Molecular genetics:
CDKN2A gene (chromosomal locus 9p21)
In several families of Mediterannean origin the same mutation was found V59G among those three families were of Jewish origin one from Morocco and the other two from Tunisia.

References:
Yakobson E, Eisenberg S, Isacson R, Halle D, Levy-Lahad E, Catane R, Safro M, Sobolev V, Huot T, Peters G, Ruiz A, Malvehy J, Puig S, Chompret A, Avril MF, Shafir R, Peretz H, Paillerets BB. A single Mediterranean, possibly Jewish, origin for the Val59Gly CDKN2A mutation in four melanoma-prone families. Eur J Hum Genet. 2003;11:288-1296.

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 leads 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 gets to a vegetative stage at the age 3-5 and dies soon afterward.

Epidemiology:
The disease has been found to be frequent among Jews originating from Yemen and in particular from the isolate of Habban (1:75 live births in the Habbanite Jews).

Molecular genetics:
ARSA gene (chromosomal locus 22q13.31-qter)
All the Jewish patients from Habban or from Yemen are homozygotes for the same mutation P377L which occurred on the background of the PD allele.

Problems in diagnosis
The diagnosis is based on the determination of arylsulfatase A activity in leukocytes or fibroblasts. In heterozygotes, approximately 50% of normal activity of the enzyme may be found in leukocytes or fibroblasts; however a potential problem in heterozygote detection by this method is the high frequency of the pseudodeficiency allele in the general population, which leads to low in-vitro aryl sulfatase A levels without clinical manifestations. This problem is particularly relevant in the Yemenite Jews in which the frequency of the PD allele is high. There is no biochemical technique to delineate between the carriers of metachromatic leukodystrophy and those of the pseudodeficiency allele, but molecular analyses are currently suitable for this diagnosis. Among the Yemenite Jews with low arylsulfatase A deficiency the demonstration of the existence of homozygosity for the PD allele is not enough to exclude the diagnosis of an atypical form of MLD because of the existence of the MLD mutation on the PD allele.

References:
Zlotogora J, Bach G, Barak Y, Elian E. Metachromatic leukodystrophy in the Habbanite Jews: high frequency in a genetic isolate and screening for heterozygotes. Am J Hum Genet 1980;32:663-669.
Zlotogora J, Gieselmann V, Bach G. Molecular basis of late infantile metachromatic leukodystrophy in the Habbanite Jews. Hum Mutation 1995;5:137-143.

3-methylcrotonyl-coenzyme A carboxylase deficiency

Autosomal recessive (MIM 210200)
Hypotonia is usually the initial symptom.
Plasma carnitine was severely deficient, and urinary organic acid analysis revealed increased excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine.
3-Methylcrotonyl-coenzyme A carboxylase activity was reduced in skin fibroblasts; pyruvate carboxylase and serum biotinidase activities.

Epidemiology:
Four siblings were reported from a nonconsanguineous Tunisian-Jewish family

Molecular genetics:
3-Methylcrotonyl-coenzyme A carboxylase gene (chromosomal locus 3q25-q27)

References:
Elpeleg ON, Havkin S, Barash V, Jakobs C, Glick B, Shalev RS. Familial hypotonia of childhood caused by isolated 3-methylcrotonyl-coenzyme A carboxylase deficiency. J Pediatr 1992;121:407-410.

3-Methyl glutaconic aciduria - type III (Costeff syndrome)

Autosomal recessive (MIM 258501)
Bilateral optic atrophy is present in all the patients and causes a visual impairment with a decreased distance acuity that does not seem to be progressive. The electroretinogram is normal and in many cases a prolonged latency of the visual evoked potentials is found. All the patients present with neurological signs and most show pathologic findings related to the extrapyramidal system. Many of the affected children present with an early movement disorder in which chorea predominates, in some severe enough to compromise stable ambulation. Some of the patients develop spastic paraparesis after the age of 6 which may be progressive; most patients develop spasticity or hypereflexia in the lower extremities. Mild, non progressive ataxia is common sometimes with dysarthria. The intelligence may be normal but most patients have a low borderline intelligence up to mild mental retardation.

Epidemiology:
The calculated incidence is 1:10,000 among Iraqi Jews. All the families reported originated from Baghdad. In a screening of 85 adults 8 were carriers (1:10).

Biochemical defect:
3 methyl glutaconic aciduria was demonstrated in all the patients examined. The basic defect leading to the increased excretion is not known. The activity of the 3-MG-CoA hydratase was normal in cultured fibroblasts from the patients.

Molecular genetics:
OPA3 gene (chromosomal locus 19p13.3)
One unique mutation was characterized in all the Jewish patients: [OPA3, IVS1AS,G-C1].

References:
Costeff H, Gadoth N, Apter N, Prialnic M, Savir H. A familial syndrome of infantile optic atrophy, movement disorder, and spastic paraplegia. Neurology 1989; 39:595-597.
Anikser Y, Kleta R, Shaag A, Gahl AW, Elpeleg O. Type III 3 Methylglutaconic aciduria (optic atrophy plus syndrome or Costeff optic atrophy syndrome): identification of the OPA3 gene and its founder mutation in Iraqi Jews. Am J Hum Genet 2001; 69:1218-1224.

Methylenetetrahydrofolate reductase deficiency

Autosomal recessive (OMIM 236200)
The major clinical features of Homocystinuria are mental retardation, ectopia lentis, skeletal abnormalities and life threatening trombembolic events.

Molecular genetics:
MTHFR gene (chromosomal locus 19p13.3)
The mutation c.474A>T (p. G158G) is a common founder mutation among Jews of Bukharian ancestry, with an estimated carrier frequency of 1:39

References:
Ben-Shachar S, Zvi T, Rolfs A, Breda Klobus A, Yaron Y, Bar-Shira A, Orr-Urtreger A. A founder mutation causing a severe methylenetetrahydrofolate reductase (MTHFR) deficiency in Bukharian Jews. Mol Genet Metab. 2012;107:608-610.

Microcephaly with complex motor and sensory axonal neuropathy

Autosomal recessive (MIM 607596)
The disease was reported in three families and includes the combination of microcephaly peripheral neuropathy and secondary muscle atrophy. In one of the families pontocerecerebellar hypoplasia was diagnosed on MRI and the patients had central nervous system symptoms including ataxia and hypertonia. In the two other families pontocerecerebellar hypoplasia was not diagnosed and they have normal intellectual development

Epidemiology:

In a sample of 449 normal Ashkenazi Jewish controls two carriers were diagnosed and the carrier frequency is 1:225.

Molecular genetics:
VRK1 gene (chromosomal locus 14p)
The disease was reported in two families of Jewish Ashkenazi origin in both cases the patients were homozygous for R358X. The parents were related in one of the two famlies and the mutation is a founder mutation**.**

References:
Gonzaga-Jauregui C, Lotze T, Jamal L, Penney S, Campbell IM, Pehlivan D, Hunter JV, Woodbury SL, Raymond G, Adesina AM, Jhangiani SN, Reid JG, Muzny DM, Boerwinkle E, Lupski JR, Gibbs RA, Wiszniewski W. Mutations in VRK1 Associated With Complex Motor and Sensory Axonal Neuropathy Plus Microcephaly. JAMA Neurol. 2013;70:1491-1498.
Renbaum P, Kellerman E, Jaron R, Geiger D, Segel R, Lee M, King MCe Levy-Lahad E. Spinal Muscular Atrophy with Pontocerebellar Hypoplasia Is Caused by a Mutation in the VRK1 Gene. Am J Hum Genet. 2009;85:281-289.

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:
A relative high incidence of the disorder exists among Jews from Iran-Iraq.

Molecular genetics:
CHX10 gene (chromosomal locus 14q32)
A mutation in the donor-acceptor site in the first intron was found in homozygozity in a Syrian-Jewish family, but not in the Iranian Jewish family.
STRA6 gene (chromosomal locus 15q24.1)
A child born with with anophthalmia and respiratory problems was operated because of PDA was diagnosed as affected with pulmonary hypoplasia diaphragmatic hernia anophthalmia cardiac defect PDCA. The child was a compound heterozygote for two mutations [D560H/R655H].

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]
Segel R, Levy-Lahad E, Pasutto F, Picard E, Rauch A, Alteresu G, Shimmel MS. pulmonary hypoplasia diaphragmatic hernia anophthalmia cardiac defect (PDCA) syndrome due to STRA6 mutations- What are the minimal criteria? Am J Med Genet A. 2009;149A:2457-2463.
Zlotogora J, Legum C, Raz J, Merin S, BenEzra D. Autosomal recessive colobomatous microphthalmia. Am J Med Genet 1994; 49:261-262.

Mitochondrial complex I deficiency

Autosomal recessive (MIM 252010)
The patients present severe neonatal lactic academia and an isolated complex 1 deficiency

Epidemiology and molecular genetics
NDUFS6) gene (Chromosomal locus 5pter-p15.33).
The disease has been diagnosed in two Jewish families from the Caucasus. All the patients were homozygous for the mutation c.344G>A. The founder mutation was found in 2 out of 48 random Jews from the region.

References:
Spiegel R, Shaag A, Mandel H, Reich D, Penyakov Ma, Hujeirat Y, Saada A, Elpeleg O, Shalev SA. Mutated NDUFS6 is the cause of fatal neonatal lactic acidemia in Caucasus Jews. Eur J Hum Genet. 2009;17:1200-1203.

Mitochondrial complex I deficiency

Autosomal recessive (MIM 252010)
The patients present severe neonatal lactic academia and an solated complex 1 deficiency

Epidemiology and molecular genetics
NDUFS6) gene (Chromosomal locus 5pter-p15.33).
The disease has been diagnosed in two Jewish families from the Caucasus. All the patients were homozygous for the mutation c.344G>A. The founder mutation was found in 2 out of 48 random Jews from the region.

References:
Spiegel R, Shaag A, Mandel H, Reich D, Penyakov Ma, Hujeirat Y, Saada A, Elpeleg O, Shalev SA. Mutated NDUFS6 is the cause of fatal neonatal lactic acidemia in Caucasus Jews. Eur J Hum Genet. 2009;17:1200-1203.

MODY maturity onset diabetes of the young

Autosomal dominant (MIM 125851)
Glukokinase gene (Chromosomal locus 7p15-p13).
In 6 Jewish Ashkenazi Jewish families all the patients were heterozygous for the mutation c.616A>C (p.T206P). The founder mutation was found in 2 out of 48 random Jews from the region.

References:
Gozlan Y, Tenenbaum A, Shalitin S, Lebenthal Y, Oron T, Cohen O, Phillip M, Gat-Yablonski G. The glucokinase mutation p.T206P is common among MODY patients of Jewish Ashkenazi descent. Pediatr Diabetes. 2012;13:e14-21.

Mitochondrial Myopathy and sideroblastic anemia

Autosomal recessive (MIM 600462)
The patients present with myopathy, sideroblastic anemia, lactic acidosis and mental retardation.
Very low levels of cytochromes a, b, and c were detected in the patients' muscle mitochondria. Deposition of iron within the mitochondria of bone marrow erythroblasts was observed on electron microscopy. Irregular and enlarged mitochondria with paracrystalline inclusions were also seen on electron microscopy of the patients' muscle specimen.
Examination of DNA showed no deletions in the mitochondrial DNA.

Epidemiology:
The disease has been diagnosed in three Iranian Jewish families

Molecular genetics:
Pseudouridine synthase 1 gene (PUS1) gene (Chromosomal locus 12q24.33).
All the patients were homozygous for the mutation C656T.

References:
Bykhovskaya Y, Casas K, Mengesha E, Inbal A, Fischel-Ghodsian N. Missense Mutation in Pseudouridine Synthase 1 (PUS1) Causes Mitochondrial Myopathy and Sideroblastic Anemia (MLASA). Am J Hum Genet. 2004;74:1303-1308. Epub 2004 Apr 22. [Epub ahead of print]
Inbal A, Avissar N, Shaklai M, Kuritzky A, Schejter A, Ben-David E, Shanske S, Garty BZ.Myopathy, lactic acidosis, and sideroblastic anemia: a new syndrome. Am J Med Genet. 1995;55:372-378.
Zeharia A, Fischel-Ghodsian N, Casas K, Bykhocskaya Y, Tamari H, Lev D, Mimouni M, Lerman-Sagie T.Mitochondrial myopathy, sideroblastic anemia, and lactic acidosis: an autosomal recessive syndrome in persian jews caused by a mutation in the PUS1 gene. J Child Neurol. 2005; 20:449-452.

Monilethrix

Autosomal recessive (MIM 252 200)
Expression of monilethrix is variable; in mild cases, dystrophic hair may be confined to the occiput but more severely affected individuals have near total alopecia. In some cases alopecia persists throughout life; in others, regrowth of apparently normal hair may occur in adolescence or, temporarily, in pregnancy.
In rule the disorder is dominant but several families with recessive inheritance were reported among Jews.

Epidemiology:
The disease has been diagnosed in Jewish families from Irak, Iran and Morocco
The frequency of the carriers of mutations was Iraq: P267R 1:25, Iran 763delT 1:100, Morocco R289X 1:100.

Molecular genetics:
Desmoglein 4 (DSG4)(Chromosomal locus 18q).
The gene is responsible for autosomal recessive hypotrichosis
Iraqi patients P267R, Iranian patients 763delT and 216+1G>T, Morocco patients R289X

References:
Zlotogorski A, Marek D, Horev L, Abu A, Ben-Amitai D, Gerad L, Ingber A, Frydman M, Reznik-Wolf H, Vardy DA, Pras E.An Autosomal Recessive Form of Monilethrix Is Caused by Mutations in DSG4: Clinical Overlap with Localized Autosomal Recessive Hypotrichosis. J Invest Dermatol. 2006; 126:1292-1296.

Mucolipidosis III

Autosomal recessive (MIM 252605)
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 three Tunisian Jewish families

Molecular genetics:
Gamma subunit of the phosphotransferase gene (Chromosomal locus 4q21-23).
All the patients were homozygous for the mutation [500insC].

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 (Mucolipidosis III). J Clin Invest 2000; 105:573-681.

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 mucolipidosis III. J Med Genet 2004; 41:e52.

Mucolipidosis 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. Corneal opacities may be congenital but at least 30% of the patients developed the opacities only 2-4 years after birth. Retinal degeneration is usually demonstrated at the ages of 3-4 years and the process is progressive so that the patients have an extinct electroretinogram by 7-8 years. There are very few data concerning late prognosis and life expectancy is not known.

Epidemiology:
The disease is relatively frequent among Ashkenazi Jews. In Israel, the frequency of heterozygotes was found to be 1:100 in a sample of 2000 unrelated individuals. This corresponds to the estimation that was based on the detection rate of new ML IV patients annually in this ethnic group. In USA, the combined carrier frequency was 0.79%, or 1 in 127 individuals (95% CI 0.40%-1.17%).

Biochemical defect:
Abnormal lysosomal storage of gangliosides, phospholipids and mucopolysaccharides was reported in cultured fibroblasts of MLIV patients as well as in the brain biopsy of one patient and urine excretion in another patient.

Molecular genetics:
MCOLN1 gene (chromosomal locus 19p13.2-13.3)
Two mutations were characterized in Ashkenazi Jewish patients: [IVS3-1A-G], the major mutation (75-80%) and [del (EX1- EX7)], the minor mutation (20-25%).

References:
Amir N, Zlotogora J, Bach G. Mucolipidosis IV clinical spectrum and natural history. Pediatrics 1987;79:953-959.
Bargal R, Avidan N, Olender Z, Ben-Asher E, Zeigler M, Raas-Rothschild A, Frumkin A, Be-Yosef O, Friedlander Y, Lancet D, Bach G. Muculipidosis IV: Novel mutations in Jewish and non-Jewish patients and the frequency of the disease in the Ashkenazi Jewish population. Hum Mut 2001; 17:397-402.
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 mucolipidosis IV. Nat Genet 2000;26:118-121.
Edelmann L, Dong J, Desnick RJ, Kornreich R Carrier screening for mucolipidosis type IV in the American Ashkenazi Jewish population. Am J Hum Genet 2002;70:1023-1027.

Multiple cutaneous and uterine leiomyomata

Autosomal dominant (MIM 150800)
Multiple cutaneous and uterine leiomyomata syndrome (MCL) is an autosomal dominant disease characterized by the presence of concurrent benign tumors of smooth muscle origin (leiomyoma) in the skin and uterus of affected females, and in the skin of affected males. MCL can also be associated with type II papillary renal cell cancer (HLRCC).

Epidemiology:
The disease has been reported in 4 Jewish families of Iranian origin two from Tehran and 2 from Shiraz.

Molecular genetics:
Fumarate hydratase (FH) gene (chromosomal locus 1q42.3-43)
One founder mutation was found in the 4 Jewish Iranian families 905-1G>A.

References:
Chuang GS, Martinez-Mir A, Geyer A, Engler DE, Glaser B, Cserhalmi-Friedman PB, Gordon D, Horev L, Lukash B, Herman E, Cid MP, Brenner S, Landau M, Sprecher E, Garcia Muret MP, Christiano AM, Zlotogorski A.Germline fumarate hydratase mutations and evidence for a founder mutation underlying multiple cutaneous and uterine leiomyomata. J Am Acad Dermatol. 2005;52:410-416.

Multiple mitochondrial deletions

Autosomal recessive
In a family of Sephardic Jews from Libya progressive external ophthalmoparesis, skeletal muscle weakness, and Parkinsonism were observed. Autosomal recessive inheritance was suggested by many consanguineous marriages, although a dominant disorder could not be excluded. No linkage to known progressive external ophthalmoparesis locus was found. The presence of cytochrome c oxidase-negative ragged-red fibers, biochemically reduced respiratory chain complexes, and multiple mitochondrial DNA deletions in muscle biopsies from four patients suggested a new mitochondrial disorder of intergenomic communication.

References:
Casali C, Bonifati V, Santorelli FM, Casari G, Fortini D, Patrignani A, Fabbrini G, Carrozzo R, D'Amati G, Locuratolo N, Vanacore N, Damiano M, Pierallini A, Pierelli F, Amabile GA, Meco G Mitochondrial myopathy, parkinsonism, and multiple mtDNA deletions in a Sephardic Jewish family. Neurology 2001;56:802-805.

Myasthenia gravis, congenital Ic. Endplate acetyl cholinesterase deficiency

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 kyphoscolisosis. A low pupillary reaction to light is seen in the patients. The patients have a decremental EMG response on 3 to 3 Hz and a repetitive compound muscle fiber action potential that disappeared after a few stimuli at 2 to 3 Hz.
Pyridostigmine therapy is not successful.

Epidemiology:
The disease was reported in one Iraqi Jewish family.

Molecular genetics:
COLQ (chromosomal locus 3p24).
The patient was homozygous for [G240X]. The same mutation was found in several Arab patients from the region of Jerusalem.

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.

Myasthenia gravis, familial, congenital

Autosomal recessive (MIM 608931)
The most common features are ptosis, limited facial expression with a myopathic look together with mandibular prognathism, malocclusion and open bite. Facial muscular weakness is always present with bilateral ptosis but without ophthalmoplegia. Many patients have weak masticatory muscles and easy fatigability on prolonged speech. Limb involvement is rare and mild. The onset is very early, the severity is mild and there is almost no progression during the years which lead to late diagnosis. All patients have a positive Tensilon test and show improvement with pyridostigmine.

Epidemiology:
The disease was reported with an increased frequency among Jews from Iran and Iraq; the incidence in these communities is not known.

Molecular genetics:
Receptor associated protein of the synapse gene RAPSN (chromosomal locus 11p11.2-p11.1)
A same E box mutation in the RAPSN promoter was found in all the patients from Iran/Irak: -38A-->G that changes another E-box at -40 to -35 from CAACTG to CAGCTG. The same mutation was also reported in a Jewish patient of Yemenite origin.
Haplotype analysis shows that -38A-->G arises from a common founder in all the Jewish patients examined.

References:
Goldhammer Y, Blatt I, Sadeh M, Goodman RM. Congenital myasthenia associated with facial malformations in Iraqi and Iranian Jews. A new genetic syndrome. Brain 1990;113:1291-1306.
Ohno K, Sadeh M, Blatt I, Brengman JM, Engel AG. E-box mutations in the RAPSN promoter region in eight cases with congenital myasthenic syndrome. Hum Mol Genet 2003;12:739-748.

Myoneurogastrointestinal encephalopathy (MNGIE)

Autosomal recessive (MIM 603041)
Myo-neuro-gastrointestinal encephalopathy (MNGIE) is characterized clinically by the onset between the second and the fifth decade of ptosis, external ophthalmoplegia, gastrointestinal dysmotility, thin body habitus, peripheral neuropathy, myopathy, leukoencephalopathy and lactic acidosis.

Epidemiology:
The disease has been reported in at least two Ashkenazi families and some Iranian Jewish families.

Molecular genetics:
Thymidine phosphorylase gene TP (chromosomal locus 22q13.32-ter)
An Ashkenazi Jewish patient was homozygous for [E289A].
The mutation [G145R] was found in Iranian patients.

References:
Faber J, Fich A, Steinberg A, Steiner I, Granot E, Alon I, Rachmilevitz D, Freier S, Gilai A. Familial intestinal pseudo-obstruction dominated by a progressive neurologic disease at young age. Gastroenterology 1987; 92:786-789.
Haftel LT, Lev D, Barash V, Gutman A, Bujanover Y, Lerman-Sagi T. Familial mitochondrial intestinal pseudo-obstruction and neurogenic bladder. J Chil Neurol 2000; 15:386-389.
Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutation in MNGIE a human mitochondrial disorder. Science 1999; 283:689-692.

Myotonic dystrophy

Autosomal dominant (MIM 160900)

Epidemiology:
The incidence of myotonic dystrophy among Jews from Yemen is 47.3:100,000 as compared to 15.7:100,000 in the general population. This seems secondary to a high frequency of a founder premutation allele among the Yemenite Jews.

References:
Tishkoff SA, Goldman A, Calafell F, Speed WC, Deinard AS, Bonne –Tamir B, Kidd JR, Pakstis AJ, Jenkins T, Kidd KK. A global haplotype analysis of the myotonic dystrophy locus: implications for the evolution of modern humans and for the origin of myotonic dystrophy mutations. Am J Hum Genet 1998;62:1389-402.
Segel R, Silverstein S, Lerer I, Kahana E, Meir R, Sagi M, Zilber N, KorcynAD, Shapira Y, Argov Z, Abeliovich D. Prevalence of myotonic dystrophy in Israeli Jewish communities: Intercommunity variation and founder permutations. Am J Med Genet 2003;119A:273-278.

Nemaline myopathy

Autosomal recessive (MIM 256030)

Both dominant and recessive forms of nemaline or rod Myopathy have been described that cannot be distinguished on clinical or histopathologic grounds.

Epidemiology:
The disease has been reported in several Ashkenazi Jewish families. In a sample of 4090 Ashkenazi Jews (Orthodox) the carrier frequency of the mutation was 1:108.

Molecular genetics:
Nebulin gene NEB (chromosomal locus 2q22)
All the Ashkenazi Jewish patients were homozygous for a 2505 deletion including exon 55 and parts of intron 54 and 55.

References:
Anderson SL, Ekstein J, Donnelly MC, Keefe EM, Toto NR, LeVoci LA, Rubin BY. Nemaline myopathy in the Ashkenazi Jewish population is caused by a deletion in the nebulin gene. Hum Genet 2004;115:185-190.

Nephropathy and hypertension

Autosomal dominant (MIM 161900)
14 individuals in one large family were affected with an adult onset nephropathy and hypertension. All the affected individuals had either progressive renal failure and/or marked hypertension.

Epidemiology:
The family is of Iraqi Jewish origin.

Molecular genetics
The gene was mapped to 1q21 between D1S2696 and D1S2635.

References:
Cohn DH, Sohat T, Yahav M, Ilan T, Rechavi G, King L, Shohat M. A locus for an autosomal dominant form of progressive renal failure and hypertension at chromosome 1q21. Am J Hum Genet 2000;67:647-651.

Neutropenia, chronic familial

Autosomal dominant (MIM 162700)
Neutropenia of less than 2000 cells/mm3 is known to occur as a benign trait without any related disease in various ethnic groups; including Jews from Yemen and Ethiopia.
In most groups with high incidence of the trait, the skin is relatively dark and a relation between the two has been suggested. In individuals with benign neutropenia, the production of neutrophils is normal in bone marrow, it was also demonstrated that the neutropenia is not due to an excessive pooling in the marginal pool of the circulation. In addition, neutropenic subjects have been showed to be able to release cells from the bone marrow when challenged with exogenous corticosteroids or during pregnancy.

Epidemiology:
Benign neutropenia is found in approximately 25% of the Yemenites Jews and 40% of the Jews from Ethiopia.

Molecular genetics:
No studies have been reported yet

References:
Berrebi A, Melamed Y, Van Dam U. Leukopenia in Ethiopian Jews. New Eng J Med 1987;316:549.
Shoenfeld Y, Weinberger A, Avishar R, Zamir R, Gazit E, Joshua H, Pinkhas J. Familial leukopenia among Yemenite Jews. Isr J Med Sci 1978;14:1271-1274.
Shoenfeld Y, Alkan ML, Asaly A, Carmeli Y, Katz M. Benign familial leukopenia and neutropenia in different ethnic groups. Eur J Haematol 1988;41:273-277.

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.

Molecular genetics:
HAX1 (chromosomal locus 1q21.3)
In two patients from an Ashkenazi family a homozygous mutation was characterized c. 121-125 insG). While the parents were not related, the haplotype of the patients was similar (32 MBs)

References:
Smith BN, Ancliff PJ, Pizzey A, Khwaja A, Linch DC, Gale RE. Homozygous HAX1 mutations in severe congenital neutropenia patients with sporadic disease: a novel mutation in two unrelated British kindreds. British Journal Hematology 2008;144 762-770.

Niemann-Pick type A, B disease

Autosomal recessive (MIM 257200)
In Niemann-Pick type A (NPA), the most prominent symptom is massive hepatosplenomegaly that may be congenital or detected in early infancy. Generally, the developmental course of these infants is normal up to the age of 3-4 months. 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. Death occurs in general before the age of 3 years.

Epidemiology:
NPA is found with a relatively high frequency among Ashkenazi Jews (1:40,000). In a recent screening among Ashkenazi Jews in the USA it was found that the carrier frequency is 1:80.

Biochemical defect:
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.

Molecular genetics
SPMD1 gene (chromosomal locus 11p15.4-p15.1)
Three mutations have been found among Ashkenazi Jewish patients: [R496L], [L302P] and [fsP330]. These mutations account for more than 95% of the mutant alleles in this population.

References:
Levran O, Desnick RJ, Schuchmann EH. A frequent missense mutation in the acid sphingomyelinase gene of Ashkenazi Jewish type A and B patients. Proc Nat Acad Sci 1992;88:3748-3752.
Levran O, Desnick RJ, Schuchman EH. Identification and expression of a common missense mutation (L302P) in the acid sphingomyelinase gene of Ashkenazi Jewish type A Niemann-Pick disease patients. Blood 1992; 80:2081-2087.
Levran O, Desnick RJ, Schuchman EH Type A Niemann-Pick disease: a frameshift mutation in the acid sphingomyelinase gene (fsP330) occurs in Ashkenazi Jewish patients. Hum Mutat 1993;2:317-319.

Oculopharyngeal muscular dystrophy (OPMD)

Autosomal dominant (MIM 164300)
The characteristic clinical symptoms are ptosis and dysphagia. In rule both appear late in life and are progressive. In most patients in the 5th or 6th decade at least one of the symptoms is present. The ptosis is always bilateral, but there may be some asymmetry. Later, external ophthalmoplegia may become apparent. In the late stage of the disease the eyelids become thinner and almost transparent. The dysphagia is progressive, first for solids and then also for liquids, and may lead to malnutrition. Many patients present also with weakness of other muscles such as facial, sternocleidomastoid and of the limbs. In muscle biopsies intranuclear tubofilamentous inclusion bodies seem to be pathognomonic for the disorder.

Epidemiology:
The disorder is frequent among Jews from Uzbekistan and the incidence was estimated to be 1:700 in this community. It has been estimated that the high frequency is due to a founder effect that appeared or was introduced in the Bukhara Jewish population between 872 and 1512.

Molecular genetics
Protein2 gene PABP2 (chromosomal locus 14q11.2-q13)
The polyA biding protein 2 gene PABP2 encodes for a (GCG) repeat that is expanded in this disease. The expansion is between 8 to 13 repeats. The compound heterozygotes for the expansion and a normal allele with 7 repeats are more severely affected.

References:
Blumen SC, Korczyn AD, Lavoie H et al. Oculophayngeal muscular dystrophy among Bukhara Jews is due to a founder (GCG)9 mutation in the PABP2 gene. Neurol 2000; 55:1267-1270.
Blumen SC, Nisipeanu P, Sadeh M et al. Clinical features of oculophayngeal muscular dystrophy among Bukhara Jews. Neuromusc Disorders 1993;3:575-577.
Brais B, Bouchard JP, Xie YG, Rochefort DL, Chretien N, Tome FM, Lafreniere RG, Rommens JM, Uyama E, Nohira O, Blumen S, Korcyn AD, Heutink P, Mathieu J, Duranceau A, Codere F, Fardeau M, Rouleau GA. Short GCG expansions in the PABP2 gene cause oculopharyngeal muscular dystrophy. Nat Genet 1998;18:164-167.

Omenn syndrome

Autosomal recessive (MIM 603554)
Omenn syndrome is a severe immunodeficiency characterized by the presence of activated, anergic, oligoclonal T cells, hypereosinophilia, and high IgE levels, have missense mutations in either the RAG1 or RAG2 genes that result in partial activity of the 2 proteins.
The syndrome is characterized by T-cell infiltration of skin, gut, liver, and spleen, leading to diffuse erythroderma, protracted diarrhea, failure to thrive, and hepatosplenomegaly. The lesions resembled those in graft-versus-host diseases.

Epidemiology:
The disorder was reported in two Jewish families of Georgian and Iraqi origin.

Molecular genetics
RAG 2 gene (Chromosome locus 11p13)
In the two Jewish patients the same mutation c.C1886T was characterized (p.Arg229Trp)

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.

Ornithine aminotransferase deficiency

Autosomal recessive (MIM 258870)
The clinical history of gyrate atrophy of the choroid and retina is usually night blindness that begins in late childhood, accompanied by sharply demarcated circular areas of chorioretinal atrophy. During the second and third decades the areas of atrophy enlarge.

Epidemiology:
The disorder was reported in one Iraqi Jewish family.

Biochemical defect:
Ornithine-delta-aminotransferase catalyzes the major catalytic reaction for ornithine. Ornithinemia presumably due to deficiency of ornithine ketoacid aminotransferase (OAT) is found in the patients with gyrate atrophy of the choroid and retina.

Molecular genetics
Ornithine ketoacid aminotransferase gene OAT (chromosomal locus)
In an Iraqi Jewish patient the deletion of cytosine at position 159 in the OAT gene resulted in a frameshift.

References:
Mitchell G, Brody , Sipila I, Simell O, Engelhardt J, Martin L, Steel G, Obie C, Fontaine G, Kaiser-Kupfer M, Valle D. Mutational analysis of ornithine-delta-aminotransferase (OAT) in 72 gyrate atrophy (GA) pedigrees. (Abstract) Am J Hum Gen 45: A207 only, 1989.

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.

Molecular genetics and epidemiology:
ATP6I (TC1RG1) gene encoding for a3 subunit of the vacuolar proton pump (chromosomal locus 2q36-37).
An A to T transversion in the fourth base of the intron 2 donor splice site (c.117+4A→T) in TCIRG1was reported in several Ashkenazi Jewish families. Analysis of a random sample of Ashkenazi Jews revealed a carrier frequency of approximately 1 in 350.

References:
Anderson SL, Jalas C, Fedickc A, Reid KF, Carpenter TO, Chirnomas D, Treff NR, Ekstein J, Rubin BY. A founder mutation in the TCIRG1 gene causes osteopetrosis in the Ashkenazi Jewish population. Clin Genet online 2014.

Osteoporosis-pseudoglioma syndrome

Autosomal recessive (MIM 259770)
The osteoporosis-pseudoglioma syndrome is a rare autosomal recessive disorder characterized by severe juvenile-onset osteoporosis and congenital or early-onset blindness. Other manifestations include muscular hypotonia, ligamentous laxity, mild mental retardation and seizures.

Epidemiology
The disorder was described in one Tunisian consanguineous Jewish family

Molecular genetics
Low density lipoprotein receptor-related family member LRP5 gene (chromosomal locus 11q11-12)
The patient was homozygous for R353Q

References
Lev D, Binson I, Foldes AJ, Watemberg N, Lerman-Sagie T.Decreased bone density in carriers and patients of an Israeli family with the osteoporosis-pseudoglioma syndrome. Isr Med Assoc J. 2003;5:419-421.
Ai M , Heeger S , Bartels CF , Schelling D K and the Osteoporosis-Pseudoglioma Collaborative Group. Clinical and Molecular Findings in Osteoporosis-Pseudoglioma Syndrome Am J Hum Genet 2005;77:741-753.

Otosclerosis

Autosomal dominant (MIM 166800)
Clinical otosclerosis has a prevalence of 0.2 to 1% among adults; it is characterized by isolated endochondral bone sclerosis of the labyrinthine capsule. Otosclerotic foci invade the stapedio-vestibular joint (oval window) and interfere with free motion of the stapes.
Mean age of onset is in the third decade and 90% of affected persons are under 50 years of age at the time of diagnosis. Approximately 10% of affected persons developed profound sensorineural hearing loss across all frequencies.

Epidemiology
The disorder was described in one Yemenite Jewish family

Molecular genetics
OTSC4 (chromosomal locus 16q21-23.2)

References
Brownstein Z, Goldfarb A, Levi H, Frydman M, Avraham KB. Chromosomal mapping and phenotypic characterization of hereditary otosclerosis linked to the OTSC4 locus. Arch Otolaryngol Head Neck Surg. 2006; 132:416-424.

Papillon-Lefevre syndrome (Haim-Munk syndrome)

Autosomal recessive (MIM 245010)
Among members of a small community of Jews from Cochin (India) a syndrome of congenital palmoplantar keratosis, pes planus, onychogryphosis, periodontosis, arachnodactyly, and acroosteolysis was reported. Although both PLS and HMS share the cardinal features of PPK and severe periodontitis, a number of additional findings are reported in HMS including arachnodactyly, acro-osteolysis, atrophic changes of the nails, and a radiographic deformity of the fingers. While PLS cases have been identified throughout the world,

Epidemiology
The disorder has only been described among descendants of a religious isolate originally from Cochin, India.

Molecular genetics
Cathepsin C gene gene (chromosomal locus 11q14.1-q14.3)
Papillon-Lefevre syndrome (PLS) and Haim-Munk syndrome (HMS) were associated with mutations of cathepsin C and are allelic. Among the Jews from Cochin a mutation (exon 6, 2127A--> G) that changes a highly conserved amino acid in the cathepsin C peptide was characterized.

References:
Haim S. Munk J. Keratosis palmo-plantaris congenita, with periodontosis, archnodactyly and peculiar deformity of the terminal phalanges. Brit J Derm 1965;77: 42-54.
Hart TC, Hart PS, Michalec MD, Zhang Y, Firatli E, Van Dyke TE, Stabholz A, Zlotogorski A, Shapira L, Soskolne WA. Haim-Munk syndrome and Papillon-Lefevre syndrome are allelic mutations in cathepsin C. J Med Genet; 2000;37:88-94.

Parkinson disease

Molecular genetics

LRRK2 gene (chromosomal locus 12q12)

The G2019S mutation appears to be an important cause of both familial and sporadic Parkinson's disease among Ashkenazi Jewish subjects.
Lifetime penetrance of the G2019S mutation in the Ashkenazi Jewish population was estimated of 31.8 percent.

GBA gene (chromosomal locus 1q21)

GBA is a risk factor associated with Parkinson’s disease this finding is not exclusive to a specific ethnic group or a specific GBA mutation. Since mutations in GBA are frequent among Ashkenzi Jews mutations in GBA represent a significant risk factor in this community.

VPS35 gene (chromosomal locus 1q21)

The mutation c.1858G>A; p.Asp620Asn was found as a dominant mutation associated with Parkinson disease in several families of different orgin including a Yemmenite Jewish family

References

Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2004;4;351:1972-1977.
Thaler A, Ash E, Gan-Or Z, Orr-Urtreger A, Giladi N. The LRRK2 G2019S mutation as the cause of Parkinson's disease in Ashkenazi Jews. J Neural Transm 2009;116:1473-1482.
Vilariño-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lincoln SJ, Soto-Ortolaza AI, Cobb SA, Wilhoite GJ, Bacon JA, Behrouz B, Melrose HL, Hentati E, Puschmann A, Evans DM, Conibear E, Wasserman WW, Aasly JO, Burkhard PR, Djaldetti R, Ghika J, Hentati F, Krygowska-Wajs A, Lynch T, Melamed E, Rajput A, Rajput AH, Solida A, Wu RM, Uitti RJ, Wszolek ZK, Vingerhoets F, Farrer MJ. VPS35 Mutations in Parkinson Disease. Am J Hum Genet. 2011; 89:162-167.

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 is 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 Yemenite Jewish family

Molecular genetics
Parkin gene (chromosomal locus 6q25.2-q27)
The patients were homozygous for a deletion of exon 3.

References
Nisipeanu P, Inzelberg R, Blumen SC, Carasso RL, Hattori N, Matsumine H, Mizuno Y.Autosomal-recessive juvenile parkinsonism in a Jewish Yemenite kindred: mutation of Parkin gene. Neurology. 1999 53:1602-1604.

Peeling skin syndrome

Autosomal recessive (MIM 270300)
Two main subtypes of peeling skin syndrome, noninflammatory type A and inflammatory type B, have been suggested. In some families, an acral form of peeling skin syndrome has been reported, in which skin peeling is strictly limited to the dorsa of the hands and feet but ultrastructural and histologic analyses show, as in the generalized form of the disorder, that the level of blistering is high in the epidermis at the stratum granulosum-stratum corneum junction.

Epidemiology and Molecular genetics
CDSN gene (chromosomal locus)
In one family from Iraq Kurdistan (parents first cousins) the patients were homozygous for c.746delG.

References
Hacham-Zadeh S, Holubar K. Skin peeling syndrome in a Kurdish family. Arch Dermatol. 1985;121:545-546
Israeli S, Zamir H, Sarig O, Bergman R, Sprecher E. Inflammatory Peeling Skin Syndrome Caused by a Mutation in CDSN Encoding Corneodesmosin. J Invest Dermatol. 2011 131:779-871.

Pentosuria

Autosomal recessive (MIM 260800)
Individuals that are homozygotes for pentosuria do not show any significant clinical symptoms, and no decrease in life expectancy is noted in these patients. Possible misdiagnosis of pentosuria as diabetes mellitus is common as the result of reducing substances in urine; however no abnormalities of glucose metabolism are demonstrable.

Molecular genetics and epidemiology:
DCXR gene (chromosomal locus 17q25.3)
Two mutations were identified, c.583ΔC and c.52(+1)G > A, The combined frequency of the two mutant DCXR alleles in 1,067 Ashkenazi Jewish controls was 0.0173, suggesting a pentosuria frequency of approximately one in 3,300 in this population. Haplotype analysis indicated that the c.52 (+1) G > A mutation arose more recently than the DCXR c.583ΔC mutation.

References:
Pierce SB, Spurrell CH, Mandell JB, Lee MK, Zeligson S, Bereman MS, Stray SM, Fokstuen S, MacCoss MJ, Levy-Lahad E, King MC, Motulsky AG.Garrod's fourth inborn error of metabolism solved by the identification of mutations causing pentosuria.Proc Natl Acad Sci U S A. 2011;108:18313-18317.
Lane AB, Jenkins T. Human L-xylulose reductase variation: family and population studies. Ann Hum Genet 1985;49:227-235.
Mizrahi O, Ser I. Essential pentosuria. Genetic of migrant and isolate populations. ed Golschmidt Baltimore, Wiliams and Wilkins 1963.

Peripheral sensory neuropathy

Autosomal recessive
Three unrelated Oriental Jewish families (two from Syria, one from Iraq) with a total of eight subjects were reported with progressive hereditary sensory neuropathy.
The parents were all unaffected and because of parental consanguinity in each of the three families it is postulated that this rare neurological disorder is transmitted in an autosomal recessive manner.

References:
Tamari I, Goodman RM, Sarova I, Hertz M, Adar R, Zvibach T. Autosomal recessive peripheral sensory neuropathy in 3 non-Ashkenazi Jewish families. J Med Genet 1980;17:424-429.

Pernicious anemia, juvenile, due to selective intestinal malabsorption of vitamin B12 with proteinuria

Autosomal recessive (MIM 261100)
The patients present early in life with symptoms of megaloblastic anemia that is quite severe. In addition, most patients have also moderate leukopenia and thrombocytopenia. All patients have proteinuria.
The response to treatment, namely intramuscular injection of vitamin B12, is dramatic. Parenteral injections of vitamin B12 are a lifetime treatment.

Epidemiology:
The disease is very rare. It was reported with an increased incidence in Scandinavian countries and among Sepharadic Jews. The incidence among Jews from Tunisia has been estimated in 1969 to be 1:1600 live births.
While among Finnish patients mutations were found in the gene CUBILIN among Norwegian and Jewish patients from Tunisia mutations were found in the Amnionless mouse homolog AMN gene.

Molecular genetics:
Amnionless mouse homolog AMN gene (chromosomal locus 14q32)
In the families of Tunisian Jewish origin the patients were homozygous for a change from CAG to CGG in the acceptor splice site of intron 3 [208-2A-G] of the AMN gene and skipping of exon 4. The mutation appears to be very old and was found in two Turkish families (same old haplotype).
In a Jewsih family the Ashkenazi father of a patient of mixed Jewish/non Jewish origin the mutation was c.43+1G>T; splice site

Cubilin Gene
In two Ahkenazi Jewish families the patients were homozygous for c.2624_2615delGA

References:
Ben-Bassat I, Feinstein A, Ramot B. Selective vitamin B12 malabsorption with proteinuria in Israel: clinical and genetic aspects. Israel J Med Sci 1969;5:62-68.
Luder AS, Tanner SM, de la Chapelle A, Walter JH. Amnionless (AMN) mutations in Imerslund-Gräsbeck syndrome may be associated with disturbed vitamin B(12) transport into the CNS. J Inherit Metab Dis. 2008 Jan 7 [Epub ahead of print]
Tanner SM., Li Z, Bisson R Acar C, Öner C, Öner R, Çetin M, Abdelaal MA, Ismail EA, Lissens W, Krahe R, Broch H, Gräsbeck R, de la Chapelle A**.** Genetically heterogeneous selective intestinal malabsorption of vitamin B_{12}: Founder effects, consanguinity, and high clinical awareness explain aggregations in Scandinavia and the Middle East Hum Genet 2004;23:327-333.
Tanner SM, Sturm AC, Baack EC, Liyanarachchi S and de la Chapelle A. Inherited cobalamin malabsorption. Mutations in three genes reveal functional and ethnic patterns. Orphanet Journal of Rare Diseases 2012,7:56

Persistent hyperinsulinemic hypoglycemia of infancy PHHI (familial hyperinsulinism)

Autosomal recessive (MIM 600509)
The disease is characterized by profound hypoglycemia in infancy. It causes seizures, coma and may be lethal or result of irreversible neurologic sequel in absence of treatment.
The combination of a paternally inherited germline mutation and somatic loss-of-heterozygosity causes the focal form of the disease (Focal-congenital hyperinsulinism of infancy [Focal-CHI]). The risk for a carrier that inherited the allele from his father is 1:270.

Epidemiology:
The disease is found with a relatively high incidence among the Ashkenazi Jews. The allele frequency of ABCC8 c.3989-9G>A and p.F1387del was examined in 21122 Ashkenazi Jews (Dor Yeshorim) and the combined mutation frequency was 1:52

Molecular genetics:
Two genes linked one to the other are found on chromosome 11p14-15.1 - Kir 6.2 and the sulfonylurea receptor gene ABCC8 (SUR1). Each gene encodes for a subunit of the pancreatic islet alpha-cell ATP sensitive potassium (KATP) channel. Two mutations in ABCC8 were associated with 88% of the HPPI chromosomes in the Ashkenazi Jews: [ABCC8, IVS32, G-A, -9 EXON ALPHA], the predominant mutation (68.8%) and [ABCC8, delta F1388].

References:
Glaser B, Blech I, Krakinovsky Y, Ekstein J, Gillis D, Mazor-Aronovitch K, Landau H, Abeliovich D. ABCC8 mutation allele frequency in the Ashkenazi Jewish population and risk of focal hyperinsulinemic hypoglycemia.Genet Med 2011;13:891-894.
Nestorowicz A, Wilson BA, Schoor KP, Inoue H, Glaser B, Landau H, Stanley CA, Thorton PS, Clement JP, Bryan J, Aguilar-Bryan L, Permutt MA. Mutations in the sulfonylurea receptor gene are associated with familial hyperinsulinism in Ashkenazi Jews. Hum Mol Genet 1996;11:1813-1822.

Peroxisome biogenesis disorders

Autosomal recessive (MIM 601539)
The firstborn son of unrelated parents, who both had sensorineural deafness and RP diagnosed as USH, presented with sensorineural deafness, RP, dysmorphism, developmental delay, hepatomegaly, and hypsarrhythmia and died at age 17 mo. The infant was shown to have a PBD, on the basis of elevated plasma levels of very-long- and branched-chain fatty acids (VLCFAs and BCFAs), deficiency of multiple peroxisomal functions in fibroblasts, and complete absence of peroxisomes in fibroblasts and liver. Surprisingly, both parents had elevated plasma levels of VLCFAs and BCFAs. Fibroblast studies confirmed that both parents had a PBD. The parents' milder phenotypes correlated with relatively mild peroxisomal biochemical dysfunction and with catalase immunofluorescence microscopy demonstrating mosaicism and temperature sensitivity in fibroblasts.

Molecular genetics:
PEX6 gene (chromosomal locus)
The father (Yemenite Jew) was homozygous for 1715C-T and the mother (Algerian/Ashkenazi) compound heterozygous for IVS10+2T-C and A809/I845T.

References:
Raas-Rothschild A, Wanders RJ, Mooijer PA, Gootjes J, Waterham HR, Gutman A, Suzuki Y, Shimozawa N, Kondo N, Eshel G, Espeel M, Roels F, Korman SH.A PEX6-defective peroxisomal biogenesis disorder with severe phenotype in an infant, versus mild phenotype resembling Usher syndrome in the affected parents. Am J Hum Genet 2002;70:1062-1068.

Phenylketonuria, hyperphenylalaninemia

Autosomal recessive (MIM 261630)

Epidemiology:
PKU is very rare among Ashkenazi Jews and relatively frequent among Jews from Yemen, the Caucasian Mountains, Bukhara and Tunisia. The disease was found with an incidence of 1:5000 among Jews from Yemen. All the families of the affected patients from Yemen originated from San'a. The possibility that the increased incidence of the disease in this population is the result of a founder effect is supported by the common origin of the patients as well as the recent molecular studies that demonstrated that all the patients have a similar deletion in the gene.

Biochemical defect:
Phenylketonuria is due to the deficiency of the enzyme phenylalanine hydroxylase (PAH) which converts phenylalanine to tyrosine. In humans, the enzyme is found only in the liver.

Molecular genetics:
PAH gene (chromosomal locus 12q24.1)
All the affected Jews from Yemen have the same mutation: a 6.7 Kb deletion spanning the third exon of the PAH gene. The mutations responsible for the high frequency were L48S for the Tunisian Jews and E178G, P281L and L48S for Jews from the Caucasian Mountains and Bukhara.

References:
Avigad S, Cohen BE, Bauer S, Schwartz G, Frydman M, Woo SLC, Niny Y, Shiloh Y. A single origin of phenylketonuria in Yemenite Jews. Nature 1990;344:168-170.
Cohen BE, Bodonyi E, Szeinberg A. Phenylketonuria in Jews. Lancet 1961;1:344-345.

Bercovich D, Elimelech A, Yardeni T, Korem S, Zlotogora J, Gal N, Goldstein N, Vilensky B, Segev R, Avraham S, Loewenthal R, Schwartz G, Anikster Y. A Mutation Analysis of the Phenylalanine Hydroxylase (PAH) Gene in the Israeli Population. Ann Hum Genet 2008;72:305-309.

3-Phosphoglycerate dehydrogenase deficiency

Autosomal recessive (MIM 601815)
The disorder was reported among children with congenital microcephaly, seizures and severe psychomotor retardation.
The disease was reported in two siblings of Ashkenazi Jewish origin.

Biochemical defect:
3-Phosphoglycerate dehydrogenase deficiency leads to a reduced capacity to synthesize serine.

Molecular genetics:
PHGDH gene (chromosomal locus)
The affected siblings were homozygote for V490M which was found in one out of 400 random Ashkenazi.

References:
Pind S, Slominski E, Mauthe J, Pearlman K, Swoboda KJ, Wilkins JA, Sauder P, Natowicz. V490M a common mutation in 3-Phosphoglycerate dehydrogenase deficiency, causes enzyme deficiency by decreasing the yield of mature enzyme. J Biochem Chemist 2002;277:7136-7143.

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 impairement and bilatreal polymicrogyria which was more proeminent in the frontal and parital lobes.
Polymicrogyria is a cerebral cortical malformation that is grossly characterized by excessive cortical folding and microscopically 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 demonstrates by finner cuts in MRI sections.

Epidemiology:
The disorder has been diagnosed in two **Karaite families**

Molecular genetics:
GPR56 (chromosome 16q12.2-21)
One mutation [W349S] was found in the two families

References:
Piao X, Chang BS, Bodell A, Woods K, Benzeev B, Topcu M, Guerrini R, Goldberg-Stern H, Sztriha L, Dobyns WB, Barkovich AJ, Walsh CA.Genotype-phenotype analysis of human frontoparietal polymicrogyria syndromes. Ann Neurol 2005;58:680-687.

Pontocerebellar hypoplasia

Autosomal recessive (MIM 607596)
Pontocerebellar hypoplasia (PCH) is classified into 2 main types based on the clinical picture and the spectrum of pathologic changes. In PCH type 1, 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:
The disorder has been diagnosed in three children from a Iraqi/Turkish, Syrian family.

Molecular genetics:
RARS (chromosome 5)
One mutation [IVS2+5 a>g] was found in the three patients.

References:
Edvardson S, Shaag A, Kolesnikova O, Gomori JM, Tarasov I, Einbinder T, Saada A, Elpeleg O. Deleterious mutation in the mitochondrial arginyl-tRNA synthetase gene is associated with ponto cerebellar hypoplasia. Am J Hum Genet 2007; 81:857-862.

Polyposis, MUTYH associated

Autosomal recessive (MIM 604933)
MUTYH associated polyposis is an autosomal recessive disorders characterized by predisposition for adenomatous polyps in the colon and the rectum. Biallelic carriers have a life time probability of colon cancer of 40-100%.

Epidemiology and Molecular genetics:
MUTYH gene (chromosome 5)
Two mutations Y179C and G396D are prevalent. Among Jews the mutations were not found among Ashkenazi either control or colon cancer affected individuals. Among North African Jews (Morocco) the carrier frequency was 4/7% (Y179C was 0.55% and G396D 4.15%).
In a large group of patietns of north African Jewish origin, the two mutations were frequent but no other mutations were found. The combined biallelic carriers of the mutations had an increased risk of colon cancer OR 17.4

References:
Lejbkowicz F, Cohen I, Barnett-Griness O, Pinchev M, Poynter J, Gruber SB, Rennert G. Common MUTYH mutations and colorectal cancer risk in multiethnic populations. Fam Cancer 2012;11:329-335.

Prader Willi/Angelman syndromes

MIM 176270 and MIM 105830
A deletion of 28kb in the region 15q11-q13 is relatively frequent among Ashkenazi Jews (1/75). This deletion includes the locus D15S63, a marker commonly used in the diagnosis of Prader Willi/Angelman syndromes.
As a result, methylation analysis of the locus D15S63 (usually used as the diagnostic tool for the syndrome) may lead to misdiagnosis in this community.

References:
Silverstein S, Lerer I, Buiting K, Abeliovich D. The 28 kb deletion spanning D15S63 is a polymorphic variant in the Ashkenazi Jewish population. Am J Hum Genet 2000;68:261-263.

Primary carnitine deficiency

Autosomal recessive (MIM 603377)
Primary carnitine deficiency is a disorder of fatty acid oxidation that can present at different ages with hypoketotic hypoglycemia and cardiomyopathy and or skeletal myopathy. The disease is suspected on reduced levels of carnitine in plasma and is confirmed by measurements of carnitine transport in the patient's fibroblast. The disorder was reported in a Jewish family of Iranian descent.

Molecular studies:
SLC22A5 gene (chromosomal locus 5q31)
A mutation R399Q was found in homozygosity in the Iranian Jewish family.

References:
Wang Y, Korman SH, Ye J, Gargus J, Gutman A, Taroni F, Garavaglia B, Longo N. Phenotype and genotype variation in primary carnitine deficiency. Genet Med 2001; 3:387-392.

Primary ciliary dyskinesia (PCD)

Autosomal recessive (MIM 242650)

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 and Molecular genetics:
DNAI2 gene (chromosomal location 17q25)
The disease was reported in two families from a consanguineous Iranian Jewish kindred. In the two Iranian Jewish families all the patients were homozygous for [IVS11+1G>A].

CCDC65 gene (chromosomal location 12q13.12))
In one family the patient was homozygote for c.876_877delAT. The mutation was found in three out of 733 controls.

Several founder mutations were found in the Ashkenazi Jewish population.The *DNAH5* [c.7502G>C] mutation (0.58%), the *DNAI2* [c.1304G>A] mutation (0.50%), and the *C21orf59* [c.735C>G] mutation (0.48%).

References:
Fedick A M, Jalas C, Treff NR, Knowles MR , Zariwala MA. Carrier frequencies of eleven mutations in eight genes associated with primary ciliary dyskinesia in the Ashkenazi Jewish population. Molecular Genetics & Genomic Medicine Article first published online: 6 DEC 2014
Horani A, Brody SL, Ferkol TW, Shoseyov D, Wasserman MG, Ta-Shma A, Wilson KS, Bayly PV, Amirav I, Cohen-Cymberknoh M, Dutcher SK, Elpeleg O, Kerem E. CCDC65 Mutation Causes Primary Ciliary Dyskinesia with Normal Ultrastructure and Hyperkinetic Cilia. PLoS One. 2013 6;8.
Knowles MR, Leigh MW, Ostrowski LE, Huang L, Carson JL, Hazucha MJ, Yin W, Berg JS, Davis SD, Dell SD, Ferkol TW, Rosenfeld M, Sagel SD, Milla CE, Olivier KN, Turner EH, Lewis AP, Bamshad MJ, Nickerson DA, Shendure J, Zariwala MA; the Genetic Disorders of Mucociliary Clearance Consortium. Exome Sequencing Identifies Mutations in CCDC114 as a Cause of Primary Ciliary Dyskinesia. Am J Hum Genet. 92:99-106.
Loges NT, Olbrich H, Fenske L, Mussaffi H, Horvath Jt, Fliegauf M, Kuhl H, Baktai G, Peterffy E, Chodhari R, Chung MKE, Rutman A, O'Callaghan C, Blau H, Tiszlavicz L, Voelkel K, Witt M, Ziętkiewicz E, Neesen J, Reinhardt R, Mitchison HM, Omran H. *DNAI2* Mutations Cause Primary Ciliary Dyskinesia with Defects in the Outer Dynein Arm. Am J Hum Genet. 2008;83:547-558.

Progressive cerebello-cerebral atrophy

Autosomal recessive
Progressive cerebello cerebral atrophy is a disorder including profound mental retardation, progressive spastic quadriplegia with joint contracture, progressive microcephaly, generalized seizures and irritability. MRI demonstrates progressive cerebellar atrophy followed by cerebral atrophy involving both white and grey matter.

Epidemiology and Molecular studies:
SepSecS gene (chromosomal location 4p15.2)
The disease has been reported in Jewish families from Morocco and from Iraq. The Jewish Iraqi patients were homozygous for c.1001A>G (p.Tyr334Cys) and those from Morocco for the mutation c.715G>A (pAla239Thre). In a sample of 261 Moroccan Jewish individuals 6 were carriers of c.1001A>G (p.Tyr334Cys) and in a sample of 127 Iraqi Jews 3 were carriers of c.715G>A (pAla239Thre)

VPS53 (chromosomal location 17p13.3)
In four Moroccan families two mutations were present c.2084A>G and c.1556+5G>A. The mutation c.2084A>G was found in 2:143 controls and 2:156 controls carried c.1556+5G>A

References:
Agamy O, Ben Zeev B, Lev D, Marcus B, Fine D, Su D, Narkis G, Ofir R, Hoffmann C, Leshinsky-Silver E, Flusser H, Sivan S, Sצll D, Lerman-Sagie T, Birk OS. Mutations disrupting selenocysteine formation cause progressive cerebello-cerebral atrophy. Am J Hum Genet. 2010;87:538-544.
Ben-Zeev B, Hoffman C, Lev D, Watemberg N, Malinger G, Brand N, Lerman-Sagie J. Progressive cerebellocerebral atrophy: a new syndrome with microcephaly, mental retardation, and spastic quadriplegia. J Med Genet 2003;40: e96.
Feinstein M, Flusser H, Lerman-Sagie T, Ben-Zeev B, Lev D, Agamy O, Cohen I, Kadir R, Sivan S, Leshinsky-Silver E, Markus B, Birk OS. VPS53 mutations cause progressive cerebello-cerebral atrophy type 2 (PCCA2). J Med Genet. 2014; 51:303-308.

Properdin deficiency

X-linked recessive (MIM 312060)
Individuals with properdin deficiency are healthy. However, they have a higher incidence of bacterial infections, in particular Neisseria meningitis and gonorrhea. Moreover, a fulminant course may be typical for this disorder.

Epidemiology:
Properdin deficiency was found with a relatively high incidence in Jews from North Africa, in particular from Tunisia. There is no estimate of the relative incidence.

Biochemical defect:
The patients are deficient for properdin that is a component of the complement system. It stabilizes the C3 convertase of the alternative complement pathway (C3b, Bb) and thus has an important enhancing regulatory activity.

Molecular studies:
PFCgene (chromosomal locus Xp11.4-p11.23)

References:
Schlesinger M, Mashal U, Levy J, Fishelson Z. Hereditary properdin deficiency in three families of Tunisian Jews. Act Paediatr 1993;82:744-747.

Proximal renal tubular acidosis pure

Autosomal dominant (OMIM 267300)
Inherited proximal renal tubular acidosis (pRTA) is commonly associated with more generalized proximal tubular dysfunctions and occasionally with other organ system defects.
Pure isolated pRTA is rare and the genetic cause for this disease is probably autosomal dominant

Epidemiology:
The disease was reported in one Syrian Jewsih family

Molecular genetics:
unknown

References:
Katzir Z, Dinour D, Reznik-Wolf H, Nissenkorn A, Holtzman E.Familial pure proximal renal tubular acidosis a clinical and genetic study. Nephrol Dial Transplant. 2008; 23:1211-1215.

Pseudocholinesterase deficiency (E1)

Autosomal dominant (MIM 177500)
Individuals with pseudocholisnesterase deficiency are healthy. However, when they are treated with the muscle relaxant suxamethonium, there is a prolonged muscular paralysis instead of the short effects of the drug.

Epidemiology:
Pseudocholinesterase deficiency was found with a high incidence in Jews from Iran and Iraq: 1:9 among Iranian Jews and 1:11 among Iraqi Jews.

Molecular studies:
BCHE (chromosomal locus 3q26.1-26.2)
The mutation D70G was found to be frequent

References:
Szeinberg A, Pipano S, Assa M, Medalie JH, Neufeld HN. High frequency of atypical pseudocholinesterase gene among Iraqi and Iranian Jews. Clin Genet 1972; 3:123-127.

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:
SCNN1 gene (chromosomal locus12p13)
An Iranian Jewish patient was homozygous 1621 C>T (R508stop) in the alpha subunit
SCNN1B gene (chromosomal locus16p13-p12)
An Ashkenazi Jewish patient was compound heterozygous for mutations in the beta subunit 647insA (Leu174fr) and 915delC (Ser263fr). The mutations were not found in a sample of 50 random individuals

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.

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 ahkenazi Jewish patient (parent first cousins) homozygous for a 36KB deletion.
SLC22A12 (chromosomal locus 11q13)
The syndrome has been reported in three Iraqi Jewish families. In two families the patients were homozygous for the mutation R406C.in the third family the patient was homozygous for G444R and heterozygote for R406C.

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 Soc Nephrol. 2010; 21:64-72. Epub 2009 Nov 19.
Dinour D, Bahn A, Ganon L, Ron R, Geifman-Holtzman O, Knecht A, Gafter U, Rachamimov R, Sela BA, Burckhardt G, Holtzman EJ. URAT1 mutations cause renal hypouricemia type 1 in Iraqi Jews. Nephrol Dial Transplant. 2010; 21:64-72.

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 three Jewish families one from Kurdisrtan, one Moroccan and one Syrian (Haleb).

Molecular genetics:
ATP6V1B1gene (chromosomal locus 2 cent-q13)
The patients were homozygous for mutation 1037C>G in the Syrian Jewish family and 1155-1156insC in the Moroccan Jewish family

References
Cohen T, Brand-Auraban A, Karshai C, Jacob A, Gay I, Tsitsianov J, Shapiro T, Jatziv S, Ashkenazi A. Familial infantile renal tubular acidosis and congenital nerve deafness: an autosomal recessive syndrome. Clin Genet. 1973;4:275-278.
Joshua B, Kaplan DM, Raveh E, Lotan D, Anikster Y. Audiometric and imaging characteristics of distal renal tubular acidosis and deafness. J Laryngol Otol. 2007;122:1-6.

Reticulosis, familial hystiocytic

Autosomal recessive (MIM 267700)
The disease was described among 11 patients in 4 Jewish families of Iranian and Iraqi origin. Parental consanguinity was found in 3 of them. The age of onset varied from 6 weeks to 36 months. All had fever, wasting, and hepatosplenomegaly. Lymph node enlargement and neurologic abnormalities were common. The most consistent laboratory findings were pancytopenia, atypical lympho- monocytoid cells in the peripheral blood, abnormal liver function tests, and increased CSF protein. Death occurred in 9 patients 2 weeks to 3 months after presentation. The longest survival was 2 years after presentation.

Incidence:
This very rare disorder has been reported in several Jewish families from Iran and one from Iraq.

Molecular studies:
The disorder appears to be heterogeneous. No molecular studies have been reported yet in Jewish families.

References:
Stark B, Hershko C, Rosen N, Cividalli G, Karsai H, Soffer D. Familial hemophagocytic lymphohistiocytosis (FHLH) in Israel. Description of 11 patients of Iranian-Iraqi origin and review of the literature. Cancer 1984; 54: 2109-2121.

Retinitis pigmentosa

Autosomal recessive
Retinitis pigmentosa (RP) is a heterogeneous group of retinal dystrophies characterized by night blindness followed by visual-field loss, often resulting in severe visual impairment. In most forms of RP, the disease process initially affects the rod photoreceptors to a more severe degree than the cones. Nonsyndromic RP can be inherited as autosomal recessive, autosomal dominant, or X-linked, mitochondrial and digenic patterns of inheritance have also been described

Molecular studies:
BBS2 gene (chromosomal locus 16q21)
In individuals of Ashkenazi Jewish descent a carrier frequencies of 0.473% (±0.0071%) was found for the c.311A>C mutation and 0.261% (±0.0064%) for the c.1895G>C mutation. In 4 families the patients with nosyndromic RP were either homozygous or compound heterozygous for the two mutations.

CERKL gene (chromosomal locus 2q31. 3)
The disorder has been reported in several Jewish families from Yemen
All the patients were homozygous for c.238+1G>A mutation. The mutation was found in heterozygosity in five of 112 Yemenite Jewish individuals, thus indicating a carrier frequency of 1:22 (4.4%; 95% confidence interval 0.2-8.7%) in this population

EYS gene (chromosomal locus 6q12)
The mutation p.Thr135LeufsX25 was found in several patients from Moroccan Jewish ancestry. This is a founder mutation found in one out of 94 controls from Moroccan Jewish origin and its age was estimated to be some 650 years.
The mutation c.8218_8219delCA mutation was found in patients from 6 families of Iraqi Jewish origin another mutation p.His2740TyrfsX27 was found in a single Iraqi Jewish allele

FAM161A gene (chromosomal locus 2p14-p15)
The disorder has been reported in several Jewish families. Two founder mutations were reported [p.Arg523X] in Libyan, Syrian, Tunisian, Bulgarian and Moroccan Jews and [p.Thr452SersX3] among Moroccan, Lybian, Bulagarian and Ahkenazi Jews.[p.Thr452SersX3] was found in 4 out of 127 controls of North African origin (1:32) and none of 108 Ashkenazi. [p.Arg523X] was not identified in 108 North African controls

DHDDS gene (chromosomal locus 1p36.11)
The disorder has been reported in several Ahkenazi Jewish families, all the patients were homozygous for the same mutation c.124A>G (p.Lys42Glu**.** The mutation was found in one out of 322 controls and in 8 out of 717 in another study (total 0.86% carrier frequency).

MAK gene (chromosomal locus 6q22)
In several Ashkenazi Jewish families the patients were homozygous for the same mutation Alu353bp insertion**.** Among 1207 Ashkenazi controls 10 were carriers 1:120

References:

Auslender N, Sharon D, Abbasi AH, Garzozi HJ, Banin E, Ben-Yosef T. A Common Founder Mutation of CERKL Underlies Autosomal Recessive Retinal Degeneration with Early Macular Involvement in the Yemenite Jewish Population. Invest Ophthalmol Vis Sci. 2007;48:5431-5438

Bandah-Rozenfeld D, Littink KW, Ben-Yosef T, Strom TM, Chowers I, Collin RW, den Hollander AI, van den Born I, Zonneveld MN, Merin S, Banin E, Cremers FP, Sharon D. Novel null mutations in the EYS gene are a frequent cause of autosomal recessive retinitis pigmentosa in the Israeli population.Invest Ophthalmol Vis Sci. 2010; 51:4387-4394.

Bandah-Rozenfeld D, Mizrahi-Meissonnier L, Farhy C, Obolensky A, Chowers I, Pe'er J, Merin S, Ben-Yosef T, Ashery-Padan R, Banin E, Sharon D.Homozygosity Mapping Reveals Null Mutations in FAM161A as a Cause of Autosomal-Recessive Retinitis Pigmentosa. Am J Hum Genet. 2010;87:382-391. Epub 2010 Aug 12.

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Roberts syndrome

Autosomal recessive (MIM 268300)

Roberts Syndrome (RBS,) is rare with prenatal and postnatal growth retardation, bilateral symmetric limb reduction and craniofacial abnormalities. Survival is poor beyond the neonatal period. Of interest, four RBS patients have been reported with neoplastic processes. At the cytogenetic level, the chromosomes present with a rod-like morphology resulting in a "railroad-track" appearance due to the absence of the primary constriction at the centromeric regions and with a "puffing" or "repulsion" localized at their heterochromatin especially of chromosomes. This phenomenon known as premature centromere separation (PCS) or heterochromatin repulsion (HR) constitutes the major diagnostic marker for RBS.

Molecular genetics and epidemiology

ESCO2 (Establishment of Cohesion 1 Homologue 2) gene (chromosomal locus8p21.1)
In one Syrian Jewish family from Haleb an affected patient homozygous for c.1674-2A>G was reported.

References

Gordillo M, Vega H, Trainer AH, Hou F, Sakai N, Luque R, Kayserili H, Basaran S, Skovby F, Hennekam RC, Uzielli ML, Schnur RE, Manouvrier S, Chang S, Blair E, Hurst JA, Forzano F, Meins M, Simola KO, Raas-Rothschild A, Schultz RA, McDaniel LD, Ozono K, Inui K, Zou H, Jabs EW. The molecular mechanism underlying Roberts syndrome involves loss of ESCO2 acetyltransferase activity. Hum Mol Genet. 2008; 17 2172-2180.

Samaritan myopathy

Autosomal recessive (MIM)
In contrast to other congenital myopathies where muscle weakness is progressive or stable the benign Samaritan congenital myopathy is characterized by an ‘‘inverse’’ course of disease. The patients are severely affected at birth and improve progressively being minimally affected at adult stage.

Epidemiology and Molecular genetics:
RYR1 gene (chromosomal locus 19q13.1)
The diaese was reported in one Samaritan family in which the patients were homozygous for c.3263A>G (p.Tyr1088Cys). The Samaritans are an ethno-religious group of 741 people living in Israel and Nablus. Ancestrally, they consider themselves as descendants of the 10 lost tribes that formed the Kingdom of Israel. The Samaritan population has the highest recorded inbreeding coefficient in human populations due to almost exclusive intra-lineage marriages.

References:
Böhm J, Leshinsky-Silver E, Vassilopoulos S, Le Gras S, Lerman-Sagie T, Ginzberg M, Jost B, Lev D, Laporte J. Samaritan myopathy, an ultimately benign congenital myopathy, is caused by a RYR1 mutation. Acta Neuropathol 2012;124:575-581

San Fillippo A (MPS IIIA)

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 Sanfilippo 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 Jewish families, in particular from North Africa and one Karaite family

Molecular genetics:
Heparan N-sulfatase gene (chromosomal locus 17q25.3)
The mutations among Jews from North Africa were [Q365X], [R182C] and [R433W] in the Karaite family

Schimke immuno-osseous dysplasia

Autosomal recessive (MIM 242900)
The disorder includes spondyloepiphyseal dysplasia with exaggerated lumbar lordosis and protruding abdomen; and renal dysfunction.

Incidence:
The disease was reported in a patient in a nonconsanguineous Ashkenazi family. In 760 DNA samples mutation in the Ashkenazi population 1 carrier was found

Molecular studies:
SMARCAL1 gene (chromosomal locus 2q34-q36)
A splice mutation (IVS4 -2 A>G) was found in the patient and two nomal siblings. The residual SMARCAL1 mRNA levels in the patient's peripheral blood were lower compared to those observed in both asymptomatic brothers' carrying the same bi-allelic mutation, while the latter had levels similar to those found in heterozygous carriers (parents and sister)

References
Dekel B, Metsuyanim S, Goldstein N,; Pode-Shakked N, Kovalski Y, Cohen Y, Davidovits M, Anikster Y. Schimke immuno-osseous dysplasia: expression of SMARCAL1 in blood and kidney provides novel insight into disease phenotype. Pediatric Research. 2008; 63:398-403

Seborrhea-like dermatitis with psoriasiform elements

Autosomal dominant (MIM 610227)
Seborrhea-like dermatosis with psoriasiform elements, including enhanced keratinocyte proliferation, parakeratosis, follicular plugging, Pityrosporum ovale overgrowth and dermal CD4 lymphocyte infiltrate.

Incidence:
The disorder has been decribed in a Moroccan Jewish family

Molecular studies:
ZNF750 gene (chromosomal locus 17q25)
The mutation [56_57 dupCC] was found in the patients

References
Birnbaum RY, Zvulunov A, Hallel-Halevy D, Cagnano E, Finer G, Ofir R, Geiger D, Silberstein E, Feferman Y, Birk OS.Seborrhea-like dermatitis with psoriasiform elements caused by a mutation in ZNF750, encoding a putative C2H2 zinc finger protein. Nat Genet. 2006; 38:749-751

Sinus bradychardia, familial

Autosomal dominant (MIM 163800)

In three Moroccan Jewish families with symptomatic familial sinus bradycardia a common mutation in the gene HCN4 was characterized
One survived a cardiac arrest, the other presented with weakness and presyncopal events

Epidemiology:
The disease was reported in three families from Casablanca, the mutation was not found in 100 random samples in Moroccan Jews

Molecular genetics:
HCN4 gene (chromosomal locus 15q24-q25)
In the 3 families the same mutation p.A485V was characterized.

References:
Laish-Farkash A, Glikson M, Brass D, Marek-Yagel D, Pras E, Dascal N, Antzelevitch C, Nof E, Reznik H, Eldar M, Luria D. A Novel Mutation in the HCN4 Gene Causes Symptomatic Sinus Bradycardia in Moroccan Jews. J Cardiovasc Electrophysiol. 2010;21:1365-1372 Jul 19.

Spinal muscular atrophy type I (SMA1)

Autosomal recessive (MIM 253300)

Epidemiology:
The disease is present with a relatively high incidence among the Egyptian Karaites in Israel. The estimated incidence was 1:400 live born in this community.

Molecular genetics:
SMN1 gene (chromosomal locus 5q12.2-q13.3)

References:
Fried K, Mundel G. High incidence of spinal muscular atrophy type I (Werdnig Hoffmann disease) in the Karaite community in Israel. Clin Genet 1977 12:250-251.

Spinal muscular atrophy typeV (distal)

Autosomal recessive (MIM 600794)
Distal hereditary motor neuropathy (dHMN) or distal spinal muscular atrophy (dSMA) is a heterogeneous group of disorders characterized almost exclusively by degeneration of motor nerve fibers, predominantly in the distal part of the limbs. One subtype, dHMN type V (dHMN-V), is transmitted by autosomal dominant inheritance and predominantly involves the hands. It is allelic with Charcot–Marie–Tooth disease 2D (CMT2D), in which a similar phenotype is associated with sensory signs

Epidemiology:
The disease is present with a relatively high incidence among the Algerian Jews (4 families).

Molecular genetics:
GARS gene (chromosomal locus 7p15)
All the patients are homozygous for G526R and have a same founder haplotype.

References:
Dubourg O, Azzedine H, Yaou RB, Pouget J, Barois A, Meininger V, Bouteiller D, Ruberg M, Brice A, LeGuern E.The G526R glycyl-tRNA synthetase gene mutation in distal hereditary motor neuropathy type V. Neurology. 2006; 66:1721-1726.

Spondyloepimetaphyseal dysplasia, Shohat type

Autosomal recessive (MIM 602557)
All the patients have a prenatal onset of severe short stature. The manifestations noted at birth include short length, distended abdomen and small chest. The lower limbs are more affected than the upper ones as reflected by the increased U/L segment ratio. Head circumference at birth is normal. Severe lumbar lordosis, mild joint hyperlaxity and severe genu valgum and waddling gaits are observed at an early age. There is no mental retardation.
The most prominent features are radiographically wide and flare epiphyseal ossification and achondroplastic like long bone changes at infancy.

Incidence:
This very rare disorder has been reported in 4 Jewish families from Iraq.

Molecular studies:
No molecular studies have been reported yet.

References:
Basel-Vanagaite L, Shohat M. Further delineation of spondyloepimetaphyseal dysplasia Shohat type and review of the literature. J Endoc Genet 1991:21-26.
Shohat M, Lachman R, Carmi R, Bar Ziv J, Rimoin DL: New form of spondyloepimetaphyseal dysplasia (SEMD) in Jewish family of Iraqi origin. Am J Med Genet 1993; 46:358-362.

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 two Jewish families one from Egypt (consanguineous) one from Iraq

Molecular genetics:
DDR2 gene (chromosomal locus 1q23)
The parents of the Jewish Egyptian patients were heterozygous for [IVS17+1g>a]

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;85:281-289.

Striate keratoderma

Autosomal dominant (MIM 125670)
Striate keratodermas (PPKS) are a rare group of autosomal dominant genodermatoses characterized by palmoplantar keratoderma typified by streaking hyperkeratosis along each finger and extending onto the palm of the hand.

Epidemiology
The disorder was described in several Jewish families.

Molecular genetics
Desmoglein gene DSG1 (chromosomal locus 18q12.1-12.2)
In one Iranian/Syrian Jewish family the patients were heterozygous [S132X], in one Yemmenite Jewish family [R26X] and in another family reported as Sepharadic Jews the mutations was [p.Q201X]. In two Ashkenazi Jewish familiesa the mutations were [p.R219X] and [p.D641fs/WT]

References
Keren H, Bergman R, Mizrachi M, Kashi Y, Sprecher E Diffuse nonepidermolytic palmoplantar keratoderma caused by a recurrent nonsense mutation in DSG1. Arch Dermatol. 2005;141:625-628.
Kljuic A, Gilead L, Martinez-Mir A, Frank J, Christiano AM, Zlotogorski A.
A nonsense mutation in the desmoglein 1 gene underlies striate keratoderma. Exp Dermatol. 2003;12:523-527.
Hershkovitz D, Lugassy J, Indelman M, Bergman R, Sprecher E. Novel mutations in DSG1 causing striate palmoplantar keratoderma. Clin Exp Dermatol. 2009;34:224-228.

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. Seizures are common after one year of age; macrocephaly progressively develops. At the age of 2 years the children are usually essentially in a vegetative state. Death occurs by 2 - 4 years.
Adult onset Tay Sachs has much more variable expression compared to the infantile type and there is no one typical course of the disease. Variability of the age of onset and the expression of the disease is found also within families. Usually, the first obvious neurological symptoms become evident by the 4th- 5th decade of life. Alternatively, the first symptoms may be psychotic abnormalities. There is a slow progression of the disease, dementia is common and eventually all the patients have muscle weakness and gluteal motor dysfunction.

Epidemiology:
The screening program for heterozygote identification among the Ashkenazi Jews established a carrier frequency of 1/27 - 1/30, which correlates with the incidence of the infantile type of 1/3600. The highest rates of carriers are found in Jews originating from central Europe. The incidence of the adult type of TSD among the Ashkenazi Jews is 1/67,000. The carrier frequency among Moroccan Jews is estimated to be 1/110 and 1:140 among Jews from Iraq.

Biochemical defect:
The infantile and adult types of the disease are caused by allelic mutations in the gene of the alpha chain of hexosaminidase A. The deficiency may be demonstrated in the serum, leukocytes or other tissues.

Molecular genetics:
alpha subunit of beta hexosaminidase gene (chromosomal locus 15q23-q24)
Three mutations in the alpha subunit of beta hexosaminidase were identified to be responsible for all the cases of infantile Tay Sachs disease among Ashkenazi Jews. The 2 most frequent mutations are 1277insTATC (73% of the mutant alleles in TSD patients) and 1421+1C (17.6% of the mutant alleles), while the third mutation [GLY269SER] is relatively rare (3.5% of the mutant alleles).
Among the Moroccan Jews, 7 mutations in the gene of the alpha chain were identified three of which were frequent: ΔF304/305 a in-frame deletion of one of the two adjacent phenylalanine codons 304 or 305 with an allele frequency of 40%, R170Q (35%) and IVS5-2 A -G (10%). The other mutation(s) were found in one allele only two of them were those found among the Ashkenazi Jews.
Among Jews from Iraq 5 mutations in HEXA were identified: +1278TATC (6%), R170Q (2%), G269S (2%), ΔF304/305 (8%), G250V (40%) while still in 40% of the allele the mutation is unknown. The G250V allele was not identified in non-Iraqi Jewish carriers.
Among Ethiopian Jews an HEXA polymorphism [V436I] was found to be common (26% of the alleles) without any influence on the HexA activity. The polymorphism is also found among Jews from other origin (Iraq, Syria, Morocco, Libya, Iran Yemen

and Eastern Europe but with a significantly lower frequency (1-7%). A high frequency of the polymorphism is also found among African American (40%).

References:

Karpati M, Peleg L, Gazit E, Akstein E, Goldman B: A novel mutation in the HEXA gene specific to Tay Sachs disease carriers of Jewish Iraqi origin. Clin Genet 2000; 57:398-400.

Kaufman M, Grinshpun-Cohen J, Karpati M, Peleg L, Goldman B, Akstein E, Adam A, Navon R. Tay Sachs disease and HEXA mutations among Moroccan Jews. Hum Mut 1997; 10:295-300.

Paw BH, Tieu PT, Kaback MM, Lim J, Neufeld EF. Frequency of the three Hex A mutant allele among Jewish and non-Jewish carriers identified in a Tay-Sachs screening program. Am J Hum Genet 1990 47:698-705.

Peleg L, Karpati L, Baram L, Zolotkovski O, Goldman B. A HexA polymorphism (V436) common to African American and Ethiopian Jews. Hum Mut Mutation and Polymorphism reports on line 2000; 211.

Thalassemia- alpha

Autosomal recessive (MIM 141800)

The disease is caused by the deficient synthesis of α-globin chains that can be either total lack or partial deficiency. Four clinical subtypes can be delineated usually correlating with the number of defective (α-globin alleles. The most severe form is hydrops fetalis which is incompatible with life since no functional α-globin chains are present. Patients either die in-utero or soon after birth. Hepatosplenomegaly, cardiac failure and hypoxia are characteristic of this form of the disease. The second type of disease is Hemoglobin H disease, in which there are three abnormal genes. Clinically, these patients vary from severe to milder manifestations characterized with jaundice, hepatosplenomegaly and hemolytic anemia. The two other subtypes are caused by one or two abnormal α-globin alleles. The clinical manifestations show a spectrum from asymptomatic individuals to mild anemia. Very few may have a more severe phenotype.

The diagnosis of hydrops fetalis and HbH disease is done by hemoglobin electrophoresis from fresh red cells lysate. Identification of the two other forms is difficult. It is best done by hemoglobin electrophoresis of cord blood, and determination of the quantity of hemoglobin Barts. Later in life, the diagnosis may be done by the demonstration of inclusion bodies in red blood cells on a blood smear stained with brilliant crezyl blue or molecular analysis.

Epidemiology:

The precise frequency of α thalassemia is extremely difficult to access due to the difficulties to identify most thalassemia individuals. Using the criterion of 4% or more of hemoglobin Barts in cord blood approximately one every 80 Kurdish Jews was found to be affected with α-thalassemia. Some very few patients are affected with HbH disease. α–thalassemia was also found with an increased frequency among Yemenites and Iraqi Jews with an estimated carrier frequency of 4% among the Yemenite Jews and a somewhat lower frequency among the Iraqi Jews. α thalassemia trait is also observed among Ashkenazi Jews with an estimated frequency of 5%.

Molecular and biochemical defect:

α-globin chains are synthesized by two adjacent identical genes on chromosome 16, thus the deficient synthesis of α-globin chains depends on the number of mutated loci. The severity is determinated by the number of non functional alleles. Among Yemenite patients, a unique deletion of 39Kb (or more) which includes both genes was identified in addition to the typical 3.7Kb deletion. In the other Jewish patients deletional and non deletional mutations have been reported.

References:

Shalmon L, Kirschmann C, Zaizov R. Alpha thalassemia genes in Israel: deletional and non deletional mutations in patients of various origins. Hum Hered 1996; 46:15-19.

Thalassemia-beta

Autosomal recessive (MIM 14900)

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 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 develops leading to hypersplenism. Leg ulcers and gallstones may be found. Treated patients present with late complications of iron deposition in particular hepatic, cardiac and endocrinologic. 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.

Epidemiology:

Beta thalassemia is found with a high frequency among the Jews originating from Kurdistan, the frequency of the carriers is estimated to be 20%. The disease is also relatively frequent among Jews from Middle Eastern countries and North Africa; the heterozygote frequency in these populations is approximately 2-4%.

Biochemical defect:

The absence or severe deficiency of beta chains lead to an excess of alpha chains which form a non functional tetramer which precipitate in the red cells forming typical inclusion bodies leading to early destruction of the red cells.

Molecular genetics:

Beta globin gene (chromosomal locus 11p15.5)

The β globin gene is the first human gene to be cloned and thus has been studied thoroughly. A total of 13 different mutations have been identified among Kurdish Jews of which are found with high frequency namely: three unique to this population, one is a frameshift 44 A → C transversion, a TATA box mutation (codon 28 A →C), a A →G transition in the last A of the cleavage polyadenylylation signal and two other mutations which are the most widely spread Mediterranean mutations: Intervening sequence 1 IVS1 nt110 (G →A) and nonsense 39.

Several mutations have been found in the Jewish Mediterranean communities.

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 ß globin mutations in Israeli ethnic groups reflects recent historic events. Am J Hum Genet 1994;54:836-843.

Rund D, Filon D, Doewling CE, Rachmilewitz E, Kazazian HH Jr, Oppenheim A. Diversity of molecular lesions causing beta thalassemia in Israel Jewish ethnic groups. in New perspectives in genetic markers and diseases among the Jewish people. Ed Adam A, Bonne Tamir B Oxford Press 1991.

Thrombastenia of Glanzmann

Autosomal recessive (MIM 283800)
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 degrees. The platelets may be seen on a blood smear prepared without an anticoagulant and the platelet count is normal. In the Jewish patients from Iraq a deficiency of the glycoprotein IIb was demonstrated.

Epidemiology:
The disease has been reported with an increased frequency among Jews from Iraq; the incidence in this community was estimated to be 1:7,700. In a sample of 700 Iraqi Jews the allele frequency of the 11bp deletion is 0.0043 and of the 11.2Kb deletion less than 0.0007.

Biochemical defect:
A deficiency or an abnormal structure of the platelet glycoprotein IIb/IIIa complex.

Molecular genetics:
The disease is caused by mutations in either glycopotein IIb or IIIa genes. Among the Iraqi Jews the most frequent mutation is a 11bp deletion in exon 12 of the GPIIIa gene (85% of the alleles). A second mutation found in this community is a 11.2Kb deletion between intron 9 and exon 14 leading to a shift in the reading frame and a stop codon (less than 8% of the alleles). A third mutation (A to G transition in the acceptor site at the 19 intron/exon junction of the GPIIb gene was described in two siblings.

References:
Yatuv R, Rosenberg N, Dardik R, Brenner B, Seligsohn U. Glanzmann thrombasthenia in two Iraqi Jewish siblings is caused by a novel splice junction mutation in the glycoprotein IIb gene. Blood Coagul Fibrinolysis 1998 9:285-288.
Rosenberg N, Yatuv R, Orion Y, Zivelin A, Peretz H, Seligsohn U. Glanzmann thrombasthenia caused by an 11.2-kb deletion in the glycoprotein IIIa (beta3) is a second mutation in Iraqi Jews that stemmed from a distinct founder. Blood 1997; 15:3654-3662.
Seligsohn U and Rososhansky. A Glanzmann's thrombasthenia cluster among Iraqi Jews in Israel. Tromb Haemostas 1984; 52:230-231.

TRMT10A dysfunction

Autosomal recessive
The patients suffered from microcephaly, intellectual disability, short stature, delayed puberty, seizures and disturbed glucose metabolism, mainly hyperinsulinaemic hypoglycaemia.

Epidemiology Molecular genetics:
TRMT10A gene (chromosomal locus 15q23-25)
The disease has been reported in one family of non consanguineous Jews from Uzbekistan. All the affected children were homozygote for Gly204Arg.

References:
Gillis D, Krishnamohan A, Yaacov B, Shaag A, Jackman JE, Elpeleg O. TRMT10A dysfunction is associated with abnormalities in glucose homeostasis, short stature and microcephaly. J Med Genet. 2014 Jul 22. [Epub ahead of print]

Tyrosinemia

Autosomal recessive (MIM 276700)
Tyrosinemia is an inborn error of metabolism due to the deficiency of the enzyme fumarylacetoacetate hydrolase. The disorder is characterized by a progressive liver disease with an increased risk of hepaocellular carcinoma, renal tubular dysfunction and porphyria like symptoms. The introduction of the herbicide NTBC has changed the outcome of most of the patients.

Epidemiology:
The disease has been reported in several unrelated Ashkenazi Jewish families.

Molecular genetics:
FAH gene (chromosomal locus 15q23-25)
All the patients were homozygous for [P261L].

References:
Elpelg O, Shaag A, Holme E, Zughayar G, Ronen S, Fisher D, Hurvitz H. Mutations analysis of the FAH gene in Israeli patients with tyrosinemia type I. Hum Mut Mutations in brief 2001 472 online.

Usher syndrome type 1

Autosomal recessive USH1B (MIM 276903)
The Usher syndromes are a group of diseases that associate retinitis pigmentosa and sensorineural deafness. Variation in the severity of the hearing loss and vestibular response among affected families distinguish between the three different genotypes.

Molecular genetics:

USH1B: *MYO7A (chromosomal locus 11q13.5)*
Among Jews from North Africa, one mutation Ala826Thr was frequent among Jewish patients from Algeria and Morocco. In addition, among patients of Moroccan Jewish origin two other mutations were also present: Gly214 Arg and 2065delC.
In one of the lineages of the Samaritans the disease is due to a stop codon mutation in MYO7A.

USH1D: *CDH23 gene (10q) MIM 605516*
The mutation G2744S was found in one sepharadic Jewish family.

USH1C: *Harmonin gene (chromosomal locus 11p15.1)*
In an Ashkenazi Jewish family (parent non related) children homozygous for the mutation 238-239insC (Frydman M). The frequency of this mutation among Ashkenazi Jews is unknown.
A founder mutation c.1220delG was found to be relatively frequent among Jews from Yemen (carrier frequency 1:119). The patients presented with late onset hearing loss.

USH1F *protocadherin-15 PCDH15 gene (chromosomal locus 10q21-q22)*
Among Ashkenazi Jews one mutation R245X is frequent: carrier frequency 0.79-2.48%.

References:
Adato A, Weil D, Kalinski H, Pel-Or Y, Ayadi H, Petit C, Korostishevsky M, Bonne-Tamir. Mutation profile of all 49 exons of the human myosin VIIA gene and haplotype analysis in Usher 1B families from diverse origins. Am J Hum Genet 1997; 61:813-821.
Ben-Yosef T, Ness SL, Madeo AC, Bar-Lev A, Wolfman JH, Ahmed ZM, Desnick RJ, Willner JP, Avraham KB, Ostrer H, Oddoux C, Griffith AJ, Friedman TB. A mutation of PCDH15 among Ashkenazi Jews with the type 1 Usher syndrome**.** N Engl J Med 2003;348:1664-1670.
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. 9386826
Khateb S, Zelinger L, Ben-Yosef T, Merin S, Crystal-Shalit O, Gross M, Banin E, Sharon D. Exome Sequencing Identifies a Founder Frameshift Mutation in an Alternative Exon of USH1C as the Cause of Autosomal Recessive Retinitis Pigmentosa with Late-Onset Hearing Loss. PLOS one 2012 e515666

Usher syndrome type 2

Autosomal recessive (MIM 276901)
The Usher syndromes are a group of diseases that associate retinitis pigmentosa and sensorineural deafness.
Type 2 Usher syndrome seems to be the most common USH type worldwide. USH2 is characterized by early onset, moderate-to-severe, stable sensorineural deafness, most pronounced at the higher frequencies. Onset of RP is postpubertal, and vestibular function is normal. However, cases of USH2 with progressive hearing loss and=or vestibular areflexia have also been described.

Molecular genetics:
USH2A *Usherin (chromosomal locus 1q41).*

- The mutation. c.12067-2A>G was found in three families originating from Bukhara. Chromosomes harboring the c.12067-2A>G mutation share the same haplotype of four polymorphic markers that span 946 kb flanking the mutation. The mutation was not detected in 54 Bukharian Jewish normal control chromosomes.
- A frameshift mutation, c.239-240insGTAC (p.T80fsX28), was found in families originating from mainly from Iraq and Iran and in single families from Afghanistan, and Yemen. Chromosomes harboring the mutation share the same haplotype that span 423 kb flanking the mutation. c.239-240insGTAC carrier frequencies of 1.9% and 3.9% were found among Iraqi and Iranian Jews, respectively. No carriers were detected among 108 Yemenite Jews.
- The nonsense mutation, c.2209C>T (p.R737X) was found in Iraqi and Kurdish (Iraqi) Jewish families. The chromosomes harboring the c.2209C>T mutation share the same haplotype that span 250 kb flanking the mutation. The carrier frequency of c.2209C>T in the Iraqi Jewish population is unknown, since no carriers were detected among 115 Iraqi Jewish control DNA samples
- In three families originating from North Africa (Morocco and Tunisia) the c.1000C>T (p.R334W) was identified. Chromosomes harboring the mutation share the same haplotype that span at least 2.6Mb flanking the mutation. The carrier frequency was 0.9% for c.1000C>T in the North African Jewish population
- The mutation c.5519G>T, (p.G1840V) was identified in a North African Jewish family. The four affected siblings in this family, were compound heterozygotes

References:
Adato A, Weston MD, Berry A, Kimberling WJ, Bonne-Tamir A. Three novel mutations and twelve polymorphisms identified in the USH2A gene in Israeli USH2 families. Hum Mutat. 2000:388
Auslender N, Bandah D, Rizel L, Behar DM, Shohat M, Banin E, Allon-Shalev S, Sharony R, Sharon D, Ben-Yosef T. Four USH2A founder mutations underlie the majority of Usher syndrome type 2 cases among non-Ashkenazi Jews. Genet Test. 2008 ;12:289-294.
Kaiserman N, Obolensky A, Banin E, Sharon D. Novel USH2A mutations in Israeli patients with retinitis pigmentosa and Usher syndrome type 2.Arch Ophthalmol. 2007; 125:219-224.

Usher syndrome type 3

Autosomal recessive (MIM276902)
The Usher syndromes are a group of diseases that associate retinitis pigmentosa and sensorineural deafness. Variation in the severity of the hearing loss and vestibular response among affected families distinguish between the three different genotypes.

Molecular genetics:
USH3:*USH3 gene (chromosomal locus 3q21-q2)*
Among Ashkenazi Jews one mutation N48K is frequent: carrier frequency 0.7% (95% CI 0-1.6%).

References:
Ness SL, Ben-Yosef T, Bar-Lev A, Madeo AC, Brewer CC, Avraham KB, Kornreich R, Desnick RJ, Willner JP, Friedman TB, Griffith AJ. Genetic homogeneity and phenotypic variability among Ashkenazi Jews with Usher syndrome type III. J Med Genet. 2003; 40:767-772.

Vesicoureteral reflux (primary)

Autosomal (MIM 193000)
Vesicoureteral reflux is the retrograde flow of urine from the bladder to the ureters and the kidneys during micturation. Usually is is isolated (primary) but also may be part of associated malformations.

The disease has been reported in 6 Ashkenazi Jewish families from the Ultraorthodox American community (Hassidic Jews)

Molecular genetics:
Linkage to 12p11-q13 in an autosomal recessive model was demonstrated in 16 families including 6 Ashkenazi Jewsih families.

References:
Weng PL, Sanna-Cherchi S, Hensle T, Shapiro E, Werzberger A, Caridi G, Izzi C, Konka A, Reese AC, Cheng R, Werzberger S, Schlussel RN, Burk RD, Lee JH, Ravazzolo R, Scolari F, Ghiggeri GM, Glassberg K, Gharavi AG.A recessive gene for primary vesicoureteral reflux maps to chromosome 12p11-q13. J Am Soc Nephrol. 2009;20:1633-1640.

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 lisencephaly type II and encephalocele has been reported in several cases. The eye abnormalities were first reported as retinal detachment but include microphthalmia, cataract, immature anterior chamber angle and retinal dysplasia with or without detachment. In addition, congenital muscular dystrophy is present in some of the patients.

Epidemiology:
The syndrome has been diagnosed in several Jewish families, in particular in several Ashkenazi Jewish families

Molecular genetics:
Several genes have been reported to be responsible for the syndrome
FCMD gene (chromosomal locus 19q13.3)
Among Ashkenazi Jews one mutation c.1167_1168insA has been reported in several families and was found in 2/299 control Ashkenazi Jews.

References:
Chemke J. Czernobilsky B. Mundel G. Barishak YR. A familial syndrome of central nervous system and ocular malformations. Clin. Genet 1975;7: 1-7.
Chung W, Winder TL, Leduc CA, Simpson LL, Millar WS, Dungan J, Ginsberg N, Plaga S, Moore SA, Chung WK. Founder Fukutin mutation causes Walker-Warburg syndrome in four Ashkenazi Jewish families. Prenat Diagn. 2009;29:560-569.
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 . Hum Mutat. 2008;29:E231-241.

Wilson disease

Autosomal recessive (MIM 277900)
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:
Wilson disease is not known to be frequent among Jews.

Molecular genetics:
ATP7B gene (chromosomal locus 13q14-q21)
Several mutations were reported:

845delT	Irani, Iraqi
H1069Q	Ashkenazi, Moroccan
E1064A	Ashkenazi
D765N	Yemenite
M645R	Ashkenazi
G1213V	Kurdish
R969Q	Libyan, Tunisian

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 stetorrhea. Hepatosplenomegaly 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 disease was first described in several siblings from a family of Iranian Jewish origin and has been has been diagnosed in several other families of the same origin.

Molecular genetics:
LIPA gene (chromosomal locus 10q24-q25)
The mutation p.G87V (alternatively G66V) was found in 5 out of 162 non affected Jews from Iran (3.086%)

References:

Valles-Ayoub Y, Esfandiarifard S, No D, Sinai P, Khokher Z, Kohan M, Kahen T, Darvish D. Wolman Disease (LIPA p.G87V) Genotype Frequency in People of Iranian-Jewish Ancestry.Genet Test Mol Biomarkers. 2011;15:395-398.

Xanthinuria

Autosomal recessive (MIM 278300)
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-olybdenum cofactor (MoCo).

Molecular genetics:
Xanthine dehydrogenase, gene XDH (chromosomal locus 2p22-23)
In an Iranian-Jewish family a 1658insC mutation in exon 16 of the XDH gene was identified

Human Molybdenum Cofactor Sulfurase (HMCS)
A non Ashkenazi patient (Roman Jew/sepharadic Jew) was a compound heterozygous for c.2326C>T (p.Arg776Cys) and a novel c.1034insA (p.Gln347fsStop379) mutation in the N-terminal domain of HMCS

References:
Levartovsky D, Lagziel A, Sperling O, Liberman U, Yaron M, Hosoya T, Ichida K, Peretz H.XDH gene mutation is the underlying cause of classical xanthinuria: a second report. Kidney Int 2000; 57:2215-2220
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. Epub 2007 Mar 23

Xeroderma pigmentosum

Autosomal recessive
The disease has been reported in several Jewish families
"The Iraqi form of XP". Several patients affected with a mild variant of xeroderma pigmentosum (12 families) have been diagnosed among Jews from Iraq and Kurdistan. The manifestations are mild and the disease is diagnosed in adulthood usually because of the skin manifestations.

Molecular genetics:
XP genes
XPD

- One Ashkenazi Jewish family R616W and D681N leading to a clinical picture of COFS cerebro-oculo-facio-skeletal syndrome

- The same founder mutation p.R683Q was found in Iraqi and Kurdistani Jewish patients with a mild form of the syndrome

XPC

- One family of Ashkenazi origin with clinical features of xeroderma pignentosum was reported.

References:
Slor H. Orgal S, Keren Z, Koka S, Bittermann Deutch O, Azizi E, Pavlotzki F, Yaniv R, Korostishevsky M, Kraemer KH, Hanawalt PC, Spivak G, Falik-Zaccai TC. A founder XPD mutation among Iraqi Jews: Estimation of the most recent common ancestor (MCRA). (Abstract/Program 1208F). Presented at the 12th International Congress of Human Genetics/61st Annual Meeting of The American Society of Human Genetics (October 14, 2011, Montreal, Canada).
Slor H, Batko S, Khan SG, Sobe T, Emmert S, Khadavi A, Frumkin A, Busch DB, Albert RB, Kraemer KH. Clinical, cellular and molecular features of an Israeli xeroderma pigmentosum family with a frameshift mutation in the XPC gene: sun protection prolongs life. J Invest Dermatol 2000;115:974-980.
Inui H, Oh KS, Nadem C, Ueda T, Khan SG, Metin A, Gozukara E, Emmert S, Slor H, Busch DB, Baker CC, Digiovanna JJ, Tamura D, Seitz CS, Gratchev A, Wu WH, Chung KY, Chung HJ, Azizi E, Woodgate R, Schneider TD, Kraemer KH. Xeroderma Pigmentosum-Variant Patients from America, Europe, and Asia. J Invest Dermatol. 2008;128:2055-2068.

Zellweger syndrome

Autosomal recessive (MIM 214100)
Zellweger syndrome is the most severe form of the peroxisome biogenesis disorders. The clinical presentation in the neonatal period include profound hypotonia, characteristic facies, seizures, inability to feed, liver cysts with hepatic dysfunction, and chondrodysplasia punctata. Infants with this condition are significantly impaired and usually die during the first year of life, having made no developmental progress. .

Epidemiology
The disease is present with a relatively high incidence among Ahkenazi Jews and the Karaites in Israel.

Molecular genetics
PEX2 (PXMP3) gene
the founder mutation c.355C>T is found with a frequency of 0.813% among the Ashkenazi Jews
All the Karaite patients are homozygous for 550delC

References
Fedick A, Jalas C, Treff NR. A deleterious mutation in the PEX2 gene causes Zellweger syndrome in individuals of Ashkenazi Jewish descent. Clin Genet 2013
Zung A, Mogilner BM, Nissani R, Appelman Z, Gelman de Kohan Z. Occurrence of cerebrohepatorenal (Zellweger) syndrome in the Karaite community in Israel: a genetic hypothesis. Isr J Med Sci 1990;26:570-572.
Singer A, Wanders RJA, Zung A, Vinler C. Founder mutation in the PEX2 (PXMP3) gene in the Jewish Karaite population in Israel.[abstract 664]. Presented at the annual meeting of The American Society of Human Genetics, October 24, 2007, San Diego, California.

Zinc deficiency, transient neonatal

Autosomal dominant (MIM 609617)
In two distinct families: females with zinc deficiency symptoms were born to non-consanguineous parents of Ashkenazi Jewish descent. The children have been exclusively breast-fed.

Molecular genetics
SLC30A2 gene
Both mothers were found to carry a heterozygous missense mutation in exon 2 which substituted a G nucleotide at position 259 to A in the coding region of ZnT-2, thereby resulting in a glycine to arginine substitution at amino acid 87 (G87R)

References
Lasry I, Seo YA, Ityel H, Shalva N, Pode-Shakked B, Glaser F, Berman B, Berezovsky I, Goncearenco A, Klar A, Levy J, Anikster Y, Kelleher SL, Assaraf YG. A dominant negative heterozygous G87R mutation in the zinc transporter, ZnT-2 (SLC30A2) results in transient neonatal zinc deficiency. J Biol Chem. 2012;287:29348-29361