Background: The application of classical and high-throughput genetic technologies has recently led to the identification of a large number of genes involved in the pathogenesis of nonsyndromic and syndromic forms of intellectual disability. Autosomal recessive forms of intellectual disability are common in Israel, mostly as a result of the high rate of consanguinity in specific isolated populations. Most genes responsible for genetic cognitive impairment are currently unknown.

Research Hypothesis: The purpose of the work was to characterize new genetic forms of intellectual disability and to identify genes that causing these syndromes.

Aims: Identification of genes causing mental retardation

Methods: We have identified several families presenting with previously undescribed forms of autosomal recessive or X-linked intellectual disability. We performed linkage analysis and/or homozygosity mapping followed by sequencing of the candidate genes. In two families we sequenced the exomes of the affected individuals by using an Illumina platform.

Results: We identified four novel genes, SOBP, UBE3B, PIGN and EIF2S3, as involved in novel human neurogenetic conditions characterized by intellectual disability and additional clinical features. SOBP gene mutation causes MRAMS syndrome, which is characterized by intellectual disability, strabismus and maxillary protrusion. In the UBE3B gene we identified mutations in three families causing a novel syndrome characterized by characteristic facial dysmorphism with blepharophimosis, ectodermal anomalies, intellectual disability and reduced cholesterol levels. In the PIGN gene we identified a homozygous disease-causing mutation in several interrelated families with intellectual disability, multiple congenital anomalies and seizures. We also showed that a novel X-chromosomal neurological disorder characterized by intellectual disability and microcephaly is caused by a missense mutation in EIF2S3 encoding the core subunit of the heterotrimeric eIF2 complex.

Conclusions: We discovered four new genes responsible for intellectual disability in humans. We also discovered a new biological mechanism causing intellectual disability by showing that a mutation in EIF2S3, which encodes a translation initiation factor, disrupts protein synthesis by promoting initiation at noncanonical start codons. This finding provides valuable clinical information and also uncovers a new tool for the study of translation regulatory mechanisms. Identification of the causative genes in our reported families will shed light on the pathogenesis of these novel neurogenetic diseases and enable identification of additional affected families worldwide. Identifying the molecular basis of severe genetic conditions may allow for genetic counseling and genetic screening.

Key words: PIGN, ID, EIF2S3, UBE3B, SOBP.
Publications associated with the project:


