Whole exome sequencing reveals complex inheritance patterns and identifies two gene mutations implicated in the development of Autism and Intellectual Disability in a consanguineous Palestinian family

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Abstract :

Despite significant heritability of autism spectrum disorders (ASDs) and intellectual disability (ID), their extreme genetic heterogeneity has proven challenging for gene discovery. The application of next generation sequencing technologies to study families with complex consanguinity proved beneficial in identifying inherited risk alleles. In this study, we apply whole exome sequencing (WES) followed by segregation analysis and phenotype-genotype correlation to study genetic changes in three siblings of a highly consanguineous Palestinian family in which parents are first cousins, and consanguineous marriages ran over the past four generations.

The three siblings presented with a neurodevelopmental phenotype that was evident in early childhood. One of the children presented with stereotypic repetitive behaviour suggestive of ASD and mild visual impairment. The second child presented with mild to moderate forms of ID and mild visual impairment, and the third child presented with the most severe phenotype including severe visual impairment, severe ID, and stereotypic and repetitive behaviours suggestive of ASD.

WES was performed for a single child, who had the most severe phenotype presenting with both ID and ASD. WES analysis revealed the presence of two homozygous pathogenic mutations. One in the gene encoding for the cyclin M2 (CNNM2), responsible for dominant hypomagnesemia, and the second in the transmembrane TMEM-163 gene. Segregation analysis in other family members confirmed that the other two affected children with the less severe phenotype had homozygous CNNM2 mutation, but not TMEM163 mutation. The parents were heterozygous for the two gene mutations.

Our results confirm that CNNM2, which was previously implicated in dominant isolated hypomagnesemia, is now causing a variable neurodevelopmental phenotype including ASD and ID when inherited in an autosomal recessive manner. The detected novel mutation is not located in the cystathionine beta synthase (CBS) domain, which is altered in structure in the dominant hypomagnesemia phenotype(Stuiver et al., 2011). Crystallography experiments indicate its possible role in changing the orientation of this domain rather than its direct structure. Taking into account the normal Magnesium blood levels in our patients, and gene expression pattern of this gene in perinatal rodent brain, our data strongly suggests a new function of this membrane protein in the developing CNS.