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Exome sequencing in 200 intellectual disability/autistic patients: new candidates and a typical presentations

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Intellectual disability (ID) and autism spectrum disorder (ASD) belong to neurodevelopmental disorders and occur in ~1% of the general population. ID and ASD often co-exist and identifying the etiology of the two conditions remains challenging due to disease heterogeneity. An accurate clinical, as well as molecular diagnosis, is essential for a deeper understanding of the pathogenesis of these conditions and for devising tailored treatments. Until the advent of the first next generation sequencing (NGS) platforms, a large fraction of cases remained not diagnosed, with many families undergoing a “diagnostic odyssey”. The introduction of exome or genome sequencing (ES/GS) has significantly improved diagnostic rates in individuals with suspected ID/ASD genetic disorders refractory to conventional diagnostic testing. Sample preparation was performed following the Nextera Flex for Enrichment manufacturer protocol. The exome sequencing analysis was performed on the Illumina NovaSeq6000 System (Illumina San Diego, CA, USA) according to the NovaSeq6000 System Guide. In the present study, ES was generated for a total of 200 individuals (84 ID and 116 ID/ASD patients). 41 pathogenic or likely pathogenic (P/LP) variants were found with a detection rate of the 22%. This study emphasizes the clinical diagnostic relevance of ES in patients with ID and/or autism with additional clinical features. Atypical phenotypic presentations were found in patients in patients with mutations in POGZ, WFS1 and SHANK3. Two candidate ID/ASD genes emerged: 1.CACNA2D1 encodes the alpha-2/delta subunit of skeletal muscle and brain voltage-dependent calcium channels. CACNA2D1 has been previously found altered in patients with epilepsy and ID. Mice-bearing point mutations in the CACNA2D1 gene have an abnormal central nervous system synaptic transmission. 2.GPR14 gene, encoding the orphan G protein-coupled receptor 14 for Urotensin II, that is widely expressed in the brain and spinal cord.

Biography

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