



Category: Clinical Genomics

Exome Sequencing for cerebral palsies: Opening windows for differential diagnosis

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Abstract

DNA sequencing technologies played a critical role in the last two decades in expanding our understanding of genetic spectrum behind neurodevelopmental disorders. Recently, induction MPS in the area of medical genetics provided chance for differential diagnosis and/or reverse phenotyping of cerebral palsies and many other developmental disorders. Here we present how ES through MPS has identified causative mutations and showed scope for further characterization of the neurodevelopmental disorders. Here we report and discuss four cases (5Y to 12Y) who were diagnosed as CP with mild or moderate ID. Whole Exome libraries were constructed using Exome RDY panel and sequenced on Ion Proton. The reads generated were aligned to *hg19* and variants were annotated and prioritized using Ion Reporter. In Cases-I & II a homozygous mutation in *PMM2* gene (NM_000303.2, c.710C>T, p.THR237ARG) and a novel nonsense mutation in gene *SLC35A2* (NM_005660.2, c.1024C>T, p.Arg342Ter) which are known to cause congenital disorder of glycosylation type Ia (MIM: 212065) and type IIm SOMATIC MOSAIC (MIM: 300896) were identified, respectively. In case-III (two male siblings) ES identified a novel Frame Shift (FS) mutation in *APRATAXIN (APTX)* gene (NM_001195248.1, c.638delG, p.Arg213fs, rs150886026) which are known to cause ATAXIA-OCULOMOTOR APRAXIA 1; AOA1 (MIM: 208920). Brain imaging in Case-IV is suggestive of Joubert syndrome with hearing loss, we identified a missense mutation in *AHII* gene (NM_001134830.1, c.2023G>A, p.Asp675Asn) and also a nonsense mutation in gene *GJB2* (NM_004004.5, c.71G>A, p.Trp24Ter) which explains the hearing impairment in the case. Mutations in cases and parent(s) were confirmed on 3500 Genetic Analyzer revealed Autosomal recessive or X-linked dominant and somatic mosaicism pattern of inheritance. Reverse phenotyping was convincing for Case I & II. Case III phenotype was delineated by the identification of responsible gene /mutation. Complex phenotype of Case IV was characterized as revealed by genotyping. Our work suggests genotype first approach will be beneficial for prompt & precise diagnosis and reverse phenotyping of neurodevelopmental disorders.

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