

Diagnostic Exome Sequencing in Adolescents with Neurological and Neurodevelopmental Disorders

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OBJECTIVE: To evaluate patterns in genetic testing and diagnostic yield in adolescents with neurological and neurodevelopmental disorders (NDD).

BACKGROUND: Diagnostic exome sequencing (DES) is increasingly utilized to identify genetic etiologies of NDD in pediatric patients. In this group, adolescents (ages 13 - 17 years) present a unique opportunity to evaluate the utility of DES in undiagnosed individuals with complex phenotypes with an extensive genetic testing history.

DESIGN/METHODS: Retrospective analysis was performed on adolescent cases tested on DES. Available clinical and genetic testing histories were reviewed for patients with neurological indications, including intellectual disability (ID)/developmental delay (DD), autism spectrum disorder (ASD), and seizures/epilepsy.

RESULTS: Analysis included 568 individuals; 258 (45%) females and 310 (55%) males. ID/DD, ASD, and seizures/epilepsy were reported in 418 (74%), 139 (24%), and 196 (35%) cases, respectively. Negative microarray, Fragile X, karyotype, fluorescence in situ hybridization (FISH), single-gene, and multi-gene panel testing (MGPT) were reported in 299 (53%), 155 (27%), 190 (33%), 123 (22%), and 33 (6%) cases, respectively. Positive or likely positive findings were identified in 106 (19%) individuals in 106 characterized genes; uncertain findings were detected in 83 (15%) individuals in 91 characterized genes. 46 (43%) positive/likely positive cases were inherited, 54 (51%) *de novo*; 34 (32%) were in autosomal recessive genes, 70 (66%) in autosomal dominant, 6 (6%) in X-linked dominant, 8 (8%) in X-linked recessive genes. In addition, 66% (70/106) of these genes are not included in a large routine neurodevelopmental MGPT. Novel findings of potential clinical relevance were identified in 5% (16/318) of trio cases.

CONCLUSIONS: DES is beneficial in diagnosing adolescents presenting with complex NDD phenotypes in which traditional testing strategies have failed to elucidate a genetic etiology. Detection of alterations in both characterized and novel genes provides patients with an accurate diagnosis and has important treatment, medical management, and reproductive implications as they transition into their adult years.