Diagnostic Exome Sequencing in Adults with Neurological Disorders

Kirsten Blanco, BS, Catherine Schultz, MS, CGC, Meghan Towne, MS, CGC

Introduction: While diagnostic exome sequencing (DES) is increasingly utilized in identifying genetic etiologies and informing medical management decisions for neurological disorders in pediatric patients, a paucity of guidelines and view that testing is primarily experimental has perpetuated a lag in adoption in the adult neurology population. Limited studies exist, and they represent small cohorts within one specialty clinic (Bardakjian et al. 2018). Herein, we report characteristics and diagnostic rates in a large cohort of adult patients with neurological disorders undergoing DES.

Methods: Clinical and genetic testing histories were reviewed for an unselected cohort of 2,127 adults (age ≥ 18 years) with neurological findings referred for DES at one commercial laboratory between January 2012 and July 2019. Patients with only one unprovoked seizure or whose neurological features were secondary to another health problem (e.g. cardiovascular involvement such as stroke) were excluded. A primary neurological indication was assigned to each patient based on available clinical histories: autism spectrum disorder only (ASD), autism spectrum disorder with intellectual disability (ASD/ID), developmental delay/intellectual disability only (DD/ID), mixed neurological phenotype (MNP), movement disorder (MD), multi-organ mixed phenotype (MMP), neurocognitive disorder (NC), neurodevelopmental disorder (NDD; seizures with ASD and/or DD/ID), neuromuscular disorder (NMD), or isolated epilepsy (EP). Overall result categories (negative, uncertain, likely positive, and positive) were determined according to predefined diagnostic variant assessment criteria and assessment of clinical overlap. Statistical analyses were performed using Fisher's exact test.

Results: Of 2,127 probands, 916 (43.1%) met the criteria for one of these clinical categories and were included in analysis; 474 (51.7%) were male and 442 (48.3%) female, with an average age at testing of 30.7 years (range 18 – 88). Overall, 869 (94.9%) patients had additional clinical findings beyond their primary neurological indication (Fig. 1).

An overall positive/likely positive report was issued to 181 (19.8%) individuals for a phenotypically-relevant positive/likely positive (P/LP) alteration in 147 characterized genes, while 163 (17.8%) patients had an uncertain overall result for inconclusive findings in 156 characterized genes. A finding in a novel candidate gene was identified in 8/457 (1.8%) patients who underwent uncharacterized gene analysis, most of which were patients with MNP (4/76, 5.3%). Negative results were reported in 564 (61.6%) patients. A P/LP result was identified in 0/5 (0.0%) patients with ASD, 13/51 (25.5%) ASD/ID, 18/66 (27.3%) DD/ID, 40/163 (24.5%) MNP, 9/102 (8.8%) MD, 55/221 (24.9%) MMP, 1/10 (10.0%) NC, 31/122 (25.4%) NDD, 10/123 (8.1%) NMD, and 4/53 (7.5%) EP patients. Patients with DD/ID, NDD, and MMP* had the highest diagnostic yields, while MD*, NMD*, and EP* were significantly less likely to have a P/LP overall result (*$p<0.05$).

In patients with previous genetic testing (714; 77.9%), the diagnostic yield was 21.1% (151/714), which is significantly higher than the diagnostic yield of patients with no reported previous testing (30/202; 16.6%) ($p=0.05$). Uninformative previous testing included microarray (475; 51.9%), fragile X analysis (179; 19.5%), karyotype (243; 26.5%), mitochondrial testing (63; 6.9%), single-gene (239; 26.1%), and multi-gene panel testing (MGPT; 222; 24.2%). Of patients with previous MGPT, 187 (84.2%) were panels for neurological indications, including epilepsy (24.1%), neurodevelopmental (18.7%), movement

(25.1%), and neuromuscular (27.3%) disorders. EMG/NCV studies and muscle biopsies were reported in 134 (14.6%) and 67 (7.3%) patients, respectively.

Of the genes with P/LP clinical overlap, 119/186 (64.0%) are associated with autosomal dominant inheritance, and 89/211 (48.0%) P/LP alterations were *de novo*. Diagnostic rates were highest in probands with informative family members available for trio analysis (134/589; 22.8%) versus 15/103 (11.2%) for duo and 30/221 (13.6%) for proband-only analysis.

Conclusion: DES is a valuable tool for diagnosing adults with neurological disorders, particularly for patients with DD/ID and complex phenotypes (NDD and MMP). The diagnostic yield for patients who had negative previous genetic testing was higher than patients who had no testing prior to DES. While parental samples may be more difficult to obtain for adult patients, trio analysis with informative family members' samples were associated with higher diagnostic rates and helped to confirm *de novo* occurrence of a result in more than a third of results. Accurate diagnosis in the adult population can aid in the identification and testing of at-risk family members, therapeutic options, and reproductive planning.