

Multi-Gene Panels vs. Diagnostic Exome Sequencing: A Comparison of Genetic Testing Options for Neurodevelopmental Disorders

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Objective: To evaluate the diagnostic yield of two genetic testing strategies used for neurodevelopmental disorders (NDD).

Background: Next generation sequencing (NGS) based multi-gene panels (MGP) and diagnostic exome sequencing (DES) have been widely used to aid in identifying disease causing mutations in NDD patients. Understanding the strengths and limitations of each test type allows providers to select the best test strategy for their patients.

Methods: A retrospective study of 128 patients with various NDD features were tested by MGP first, and then reflexed to DES. This study compared the diagnostic yield between MGP and DES in this same group of patients, and analyzed whether DES can lead to additional diagnoses.

Results: Positive results were found in 7 (5%) patients by MGP and 16 (13%) patients by DES. Among the 7 positive cases detected by MGP, reflex DES testing confirmed the same findings. Pathogenic or likely pathogenic variants were detected in 6 of the 9 remaining DES positive cases, all in genes not included on a MGP; in the final 3 cases, mutations were detected in genes not on the MGP ordered, but were on other available MGP. Variants of unknown significance (VUS) were reported in 89 (70%) MGP cases, whereas uncertain results were reported in only 25 (20%) DES cases, a significant reduction. Furthermore, negative reports were issued for 32 (25%) MGP cases and 87 (68%) DES cases.

Conclusion: While MGP provides 100% coverage in targeted genes, DES has a unique advantage of analyzing a much broader gene list, including newly reported disease genes. In this study cohort, DES achieved molecular diagnosis in an additional 9 (8%) patients who first underwent MGP testing. Phenotype-driven DES interpretation also greatly reduced the rates of uncertain results. This study provides an empirical comparison of MGP and DES and can help physicians choose the most appropriate genetic testing strategy for their patients