What you can get and what would be missed: a side by side comparison of panels vs exome testing for Neurodevelopmental disorders

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Objective: To evaluate and compare diagnostic yield and test results between two genetic testing strategies widely used for Neurodevelopmental disorders (NDD).

Background: NDD are a group of diseases that are highly clinically and genetically heterogeneous. The broad and nonspecific presentation of NDD leads to significant diagnostic challenges and new NDD loci are being discovered at a rapid pace. Identifying disease causing mutations in NDD patients helps guide clinical management. Next generation sequencing (NGS) based multi-gene panels (MGP) provide 100% coverage for targeted gene and can detected gross copy number variations by either NGS coverage analysis or by array comparative genomic hybridization (aCGH). Diagnostic exome sequencing (DES) covers >95% of the coding region, and is able to detect mutations in genes that not included in the panel. Understanding the strengths and limitations of each test type allows providers to effectively and efficiently decide which test to order in consideration of the patient's presentation, diagnostic yield, cost of testing, and turnaround time.

Methods: Our laboratory offers series reflex options from 16-gene small panel targeting high yield epilepsy gene, to 196-gene comprehensive NDD panel, to reflex DES. A retrospective study of 128 patients with various NDD features such as developmental delay, intellectual disability, autism spectrum disorder (ASD), and epilepsy were tested by MGP first, and then reflexed to DES. This study compared the diagnostic yield and test results between MGP and DES in this same group of patients. In particular, we analyzed whether DES can lead to additional diagnoses.

Results: Pathogenic mutations or likely pathogenic variants (VLPs) were detected in 7 (5%) of patients by MGP and 16 (13%) of patients by DES. Among the 7 positive cases detected by MGP, reflex DES testing was requested by ordering physician, and same positive findings were confirmed by DES. Mutations or VLPs were detected in 6 of the 9 remaining DES positive cases in genes not included on the MGP panel (*IGF1R, POMGNT1, ASXL1, KMT2A, CACNA1E and DNM1L*), and in the final 3 cases, mutations were detected in genes not in the 16-gene AutismFirst or 100-gene EpiNext panel the patient was ordered, but in the 196-gene comprehensive panel (*SLC6A8, KDM5C and HNRNPU*). In addition, three DES positive cases harbored mutations in an additional gene that is associated with patients' phenotype, but not present in any MGP (*ZBTB18, AUTS2 and CSNK2B*). Variants of unknown significance (VUS) were reported in 89 (70%) of MGP cases, and uncertain results were reported in only 25 (20%) of DES cases; a significant reduction. The significant lower uncertain result rate is mainly due to DES does not report variants that are not related to patient's phenotype. Furthermore, negative reports were issued for 32 (25%) of MGP cases and 87 (68%) of DES cases. Interestingly, in one case where the provider ordered a 22-gene Rett/Angelman panel with reflex to DES, the 22 gene MGP was able to detect a complex deletion/insertion c.1159_1214del56ins3002 in the MECP2 gene. Therefore, DES was canceled due to positive finding by MGP.

Conclusion: While MGP provides low cost, targeting to high yield genes, DES has a unique advantage of analyzing a much broader gene list which often includes newly reported disease genes, allowing novel genetic etiologies to be discovered. In this study cohort, DES achieved molecular diagnosis in additional 9 (8%) of patients who first underwent MGP testing. On the other hand, MGP has approximately 10x higher NGS coverage than DES, which allows for the detection of gross deletions and duplications, and some complex rearrangements. The overall positive yield is lower than what we previously reported for MGP (18%) and DES (33%). This is due to this study focuses on patients with initial negative MGP testing result or seeking for additional diagnosis. This study provides an empirical comparison of MGP and DES and can help physicians choose the most appropriate genetic testing strategy for their patients.

Take home message:

- While MGP provides low cost, targeting to high yield genes, DES has a unique advantage of analyzing a much broader gene list.
- DES achieved molecular diagnosis in additional 9 (8%) of patients who first underwent MGP testing.
- Higher NGS coverage in MGP allows for the detection of gross deletions and duplications, and some complex rearrangements.