Molecular diagnosis for neurodevelopmental disorders-an overview of multi-gene panels and whole exome sequencing

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OBJECTIVE: To evaluate diagnostic yield of next-generation sequencing (NGS)-based genetic testing, both multi-gene panels (MGP) and diagnostic exome sequencing (DES), for patients with neurodevelopmental disorders.

BACKGROUND: Genetic factors play a major role in developmental delay (DD), intellectual disability (ID) and autism spectrum disorders (ASD). MGP and DES have been widely used to improve the diagnostic process and to guide therapy. We compared the diagnostic yield of these two approaches for patients presenting with DD, ID, and/or ASD.

METHODS: A total of 2243 cases with a referral indication of DD, ID, and/or ASD were tested. 183 cases underwent testing with one of five targeted MGP (containing between 16 and 196 genes) for ID, ASD, or a combination. The inclusion of aCGH in MGP testing helps to identify exonic deletions/duplications, which are not detected by DES methods. The remaining 2060 cases underwent DES.

RESULTS: Of the cases that underwent MGP, pathogenic mutations were identified in 12% (22/183). Negative results were observed in 20% of cases (37/183), with the remaining 68% (124/183) found to have variants of unknown significance (VUS). Family studies to determine co-segregation were offered as follow up option to further clarify VUS. In 30 cases for which parental samples were received, 13% (4) were confirmed to be *de novo* and were reclassified as likely pathogenic, bringing the overall detection rate to date for the MGP cohort to 14%. In comparison, DES routinely included co-segregation analysis and the detection rate in characterized genes was 26.5% (598/2260).

CONCLUSIONS: MGP are useful to provide low cost, quick testing that avoids incidental findings. DES testing has the advantage of routinely identifying *de novo* alterations, novel genetic etiologies and classifying VUS by segregation information. MGP that include parental testing for co-segregation analysis can help to improve the diagnostic yield and reduce VUS rate.

Many established and new laboratory tests are available for use in patients with developmental delay, autism spectrum disorders, etc. Physicians lack a clear understanding of test methods, and test properties (e.g., sensitivity and specificity). Improved familiarity with new developments in basic science is needed to assist in the diagnosis.