

Parental co-segregation analysis significantly reduces but does not eliminate VUS rate in multi-gene panel testing

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Describe scenarios in which parental co-segregation analysis is informative for classification of variants of unknown significance (VUS) detected on multi-gene panels (MGP) for neurodevelopmental disorders.

Retrospective analysis of 79 cases in which parental co-segregation analysis was completed from July 2016-March 2017 for VUS detected on MGP. Parental samples were received after the proband report was issued. VUS in autosomal dominant (AD) and X-linked (XL) genes were eligible for parental testing. Variants were classified using a 5-tier system based on previously established algorithms. Characteristics of variants that were/were not reclassified were compared.

154 AD or XL VUS were detected among 79 cases. 54/154 VUS (35%) were downgraded to likely benign subsequent to parental testing; 6 (4%) upgraded to likely pathogenic; 94 (61%) remained VUS. The majority of downgraded variants (43/54; 80%) were inherited from an asymptomatic parent; all upgraded variants were *de novo* in the proband. Of variants that remained VUS, 35/94 (37%) lacked additional evidence for reclassification (parental segregation alone not considered sufficient); 40 (43%) were limited by gene-specific characteristics (reduced penetrance, variable expressivity, multiple inheritance patterns); 22 (23%) remained VUS due to parental phenotype or availability for testing.

Parental co-segregation analysis was informative in nearly 40% of VUS, including 4/6 variants upgraded to likely pathogenic in genes with therapeutic associations. Independent of parental results, lack of evidence on the variant and/or gene-specific characteristics limited the ability to reclassify. Further delineation of these scenarios may result in more efficient application of parental co-segregation analysis and greater yield of informative results.