Abstract Confirmation

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Title:
Parental variant study is informative for variant classification in significant number of neurodevelopment genes

Abstract:
Parental variant study (PVS) can provide powerful segregation data for variant classification. However, in genes with reduced penetrance, variable expressivity, or a non-specific associated phenotype, common in neurodevelopmental disorders, PVS may be less powerful. We sought to identify characteristics common to genes for which PVS was informative for variant classification.

Retrospective analysis of 100 cases for which PVS was completed July 2016-March 2017 for variants of unknown significance (VUS) found on multi-gene panels for neurodevelopmental disorders. Parental samples were received after the proband report was issued. VUS in autosomal dominant (AD) and X-linked (XL) genes were eligible for PVS. Variants were classified using a 5-tier system based on established algorithms. Genes in which PVS was/was not informative were compared.

179 unique VUS were found in 84 AD or XL genes. Seven VUS (4%) were upgraded to likely pathogenic (VLP), 68/179 (38%) downgraded to likely benign (VLB), 104 (58%) remained VUS. The 7 upgraded VUS were found in 5 genes: *ATP1A2, CHD2, CREBBP, KCNQ2*, *PCDH19*; all due to *de novo* event in proband. 52/68 (76%) downgraded VUS were due to informative PVS (found in asymptomatic parent); these 52 VUS were found in 33 genes. Of these 33 genes, 5 (15%) had ≥3 unique VUS downgraded per gene: *CHD8, EHMT1, FOXP1, KCNT1, PACS1*; 28 had 1-2 downgraded VUS per gene. PVS was informative for 38/104 (38%) VUS in 29 genes but VUS were not reclassified due to lack of additional supportive evidence (parental inheritance alone insufficient). PVS was not informative for 44/104 (42%) VUS found in 15 genes with multiple inheritance pattern, incomplete penetrance, variable expressivity, or non-specific disease phenotype (e.g., developmental delay, epilepsy). PVS was also not informative for 14/104 (13%) VUS inherited from a symptomatic parent, and 8 (8%) with only one parent tested.

PVS was informative for 45% (38/84) of genes with VUS and 19% (38/196) of all genes analyzed. PVS was most likely to be informative for genes associated with a well described syndrome, e.g., CHARGE, Kleefstra, Rubinstein-Taybi syndrome, or severe, early-onset phenotype, e.g., infantile epileptic encephalopathy. Understanding the types of genes for which PVS is likely to be informative may be useful for clinicians coordinating parental testing. Further understanding of the genes themselves may allow for effective variant classification using evidence not limited to PVS.

Publication Status:
The work outlined in this abstract Has not been published elsewhere.
The work outlined in this abstract Has not been accepted for future publication.

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First author's spouse/legally recognized domestic partner: None
I intend to discuss unlabeled/off-label use of FDA-approved product(s): No
I intend to discuss investigational product(s) (not FDA-approved): No

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