Parental Variant Study is Informative for Variant Classification in Significant Number of Neurodevelopment Genes

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BACKGROUND

- Parental variant study (PVS) can provide powerful segregation data for variant classification.
- However, PVS utility is limited in genes with reduced penetrance, variable expressivity, or a nonspecific associated phenotype[1], which is common in neurodevelopmental disorders.
- We sought to identify characteristics common to neurodevelopment genes for which PVS was informative for variant classification.

VARIANTS RECLASSIFIED TO LIKELY PATHOGENIC (all *de novo*)

Gene	Alteration	Molecular Diagnosis	Proband clinical summary (abbreviated)
ATP1A2	p.R937H (c.2810G>A)	ATP1A2-related neurological disorder	Teenage female: global DD, ID, autism, epilepsy syndrome (NOS), macrocephaly, dysmorphic features, melanoma, precocious puberty
CHD2	p.R1074Q (c.3221G>A)	CHD2-related neuro-developmental disorder	School-age male: generalized epilepsy, DD, behavioral problems.
CREBBP	p.R1498Q (c.4493G>A)	Rubinstein-Taybi syndrome	School-age female: autism, speech/language deficit, short stature, dysmorphic facial features/ flat facial appearance, abnormalities of fingers and toes
KCNQ2	p.Y280C (c.839A>G)	KCNQ2-related neonatal epilepsy	Toddler female: Infantile/epileptic spasms @ 12 hours of life, hypsarrhythmia variant on EEG
KCNQ2	p.R332G (c.994A>G)	KCNQ2-related neonatal epilepsy	School-age female: generalized idiopathic epilepsy @ 3 days of life, global DD/ID, cortical visual impairment, static encephalopathy, dysphagia, hypothyroidism, GERD, allergies
KCNQ2	p.V543M (c.1627G>A)	KCNQ2-related neonatal epilepsy	Infant male: myoclonic seizures @ 4 months, DD, hypotonia, lachrimal problems, short stature, external hydrocephaly on CT
PCDH19	p.R198P (c.593G>C)	PCDH19-related epilepsy	Toddler female: developmental and speech delay, dysmorphic facial features, focal seizures, asymmetric myelination on brain MRI, family history of seizures (maternal, paternal)

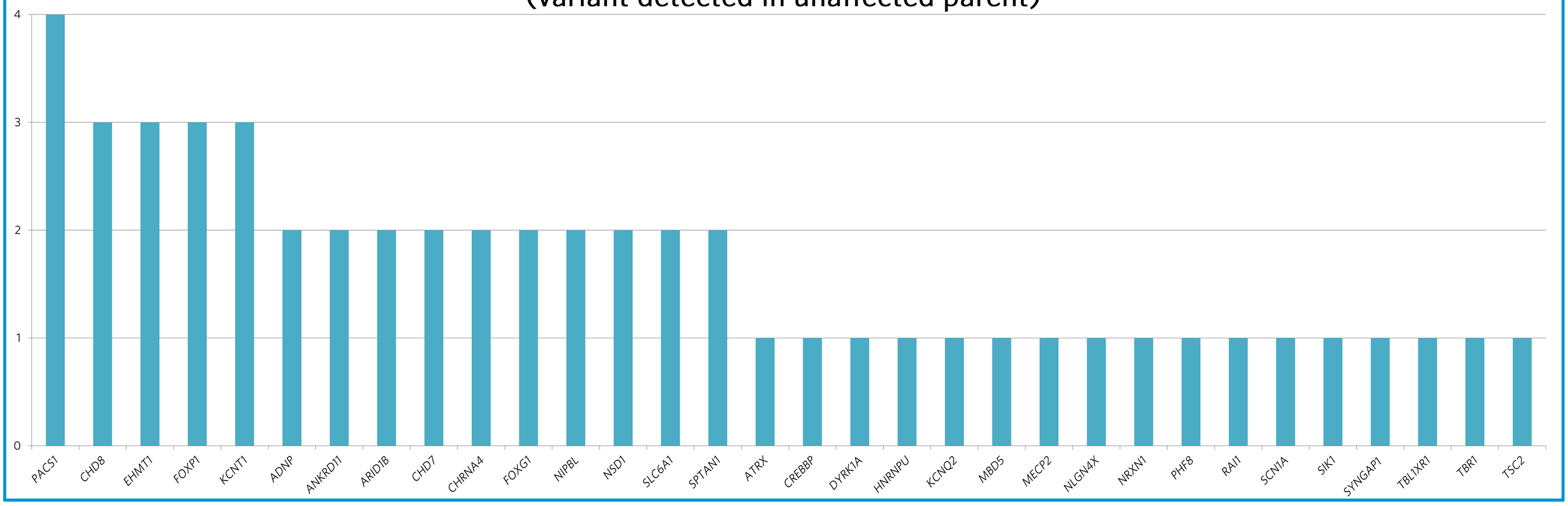
METHODS

- Retrospective analysis of 100 cases for which PVS was completed July 2016- May 2017 for variants of unknown significance (VUS) found on multigene panel tests for neurodevelopmental disorders.
- VUS in autosomal dominant (AD) and X-linked (XL) genes were eligible for PVS.
- Genes in which PVS was/was not informative were compared.

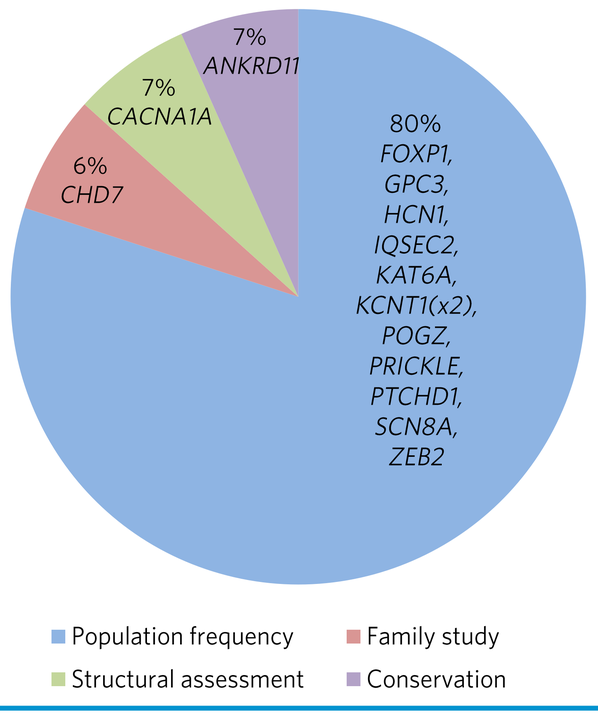
RESULTS

- 179 unique VUS found in 84 AD or XL genes.
- 7 VUS in 5 genes upgraded due to *de novo* in proband 52 VUS in 32 genes downgraded due to detected in unaffected parent.
- 15 VUS in 14 genes downgraded due to other lines of evidence.

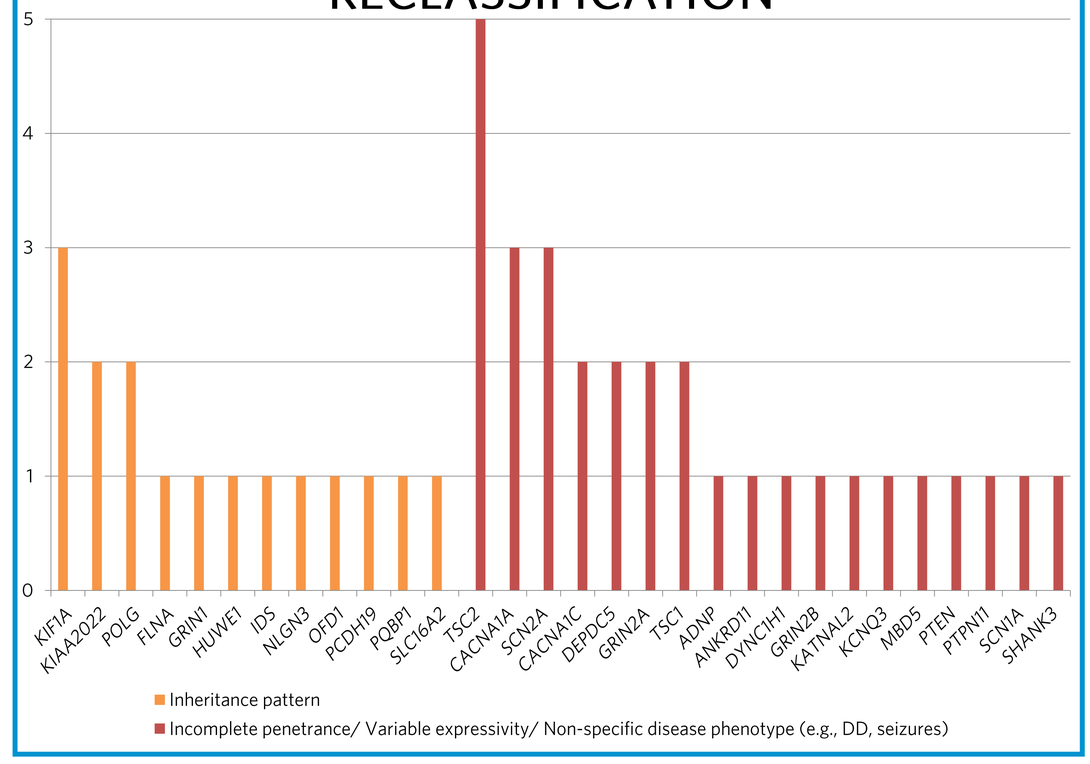
NUMBER OF VARIANTS RECLASSIFIED TO LIKELY BENIGN PER GENE (variant detected in unaffected parent)



OTHER LINES OF EVIDENCE FOR VUS DOWNGRADE TO VLB



GENE-SPECIFIC BARRIERS TO VUS RECLASSIFICATION



TAKE-HOME POINTS

- 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 or severe, early-onset phenotype.
- 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.

REFERENCES

1. Pesaran T et al. *Int J Breast Cancer.* 2016;2016:2469523. Epub 2016 Oct 16.

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