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Concurrent Parental Testing Reduces the Rate of Variants of Unknown Significance in Neurodevelopmental Multi-Gene Panels

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BACKGROUND

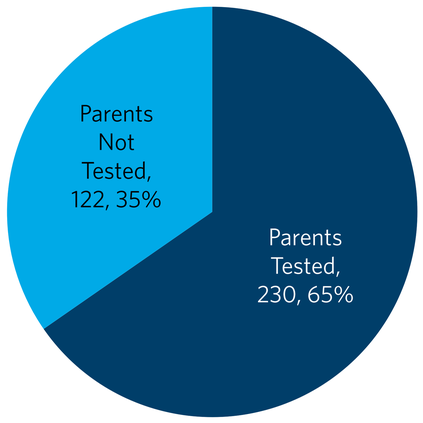
- Multi-gene panels (MGP) offer the convenience of testing multiple genes simultaneously and increase the chance of identifying disease-causing mutations.
- However, the panels can also identify a large number of variants of uncertain significance (VUS), leading to more complicated reports for patients.
- In this study, the impact of concurrent parental testing on VUS rate was evaluated in MGP for neurodevelopmental disorders.

METHODS

- Since the initial offering of upfront parental analysis in 2016, 356 consecutive cases were submitted for neurodevelopmental MGP testing with at least one parent.
- Genetic variants identified in the patients were classified to five classification tiers based on the ACMG guidelines and the classification scheme established by our laboratory.
- VUS in autosomal dominant (AD) and X-linked (XL) genes were routinely tested in available parents for co-segregation with disease.
- VUS in autosomal recessive (AR) genes were also tested in the parents when two variants (VUS or above) were detected in the same gene or multiple pathogenic variants in AR genes were detected in the patients.
- The variants were assessed before and after parental analysis.

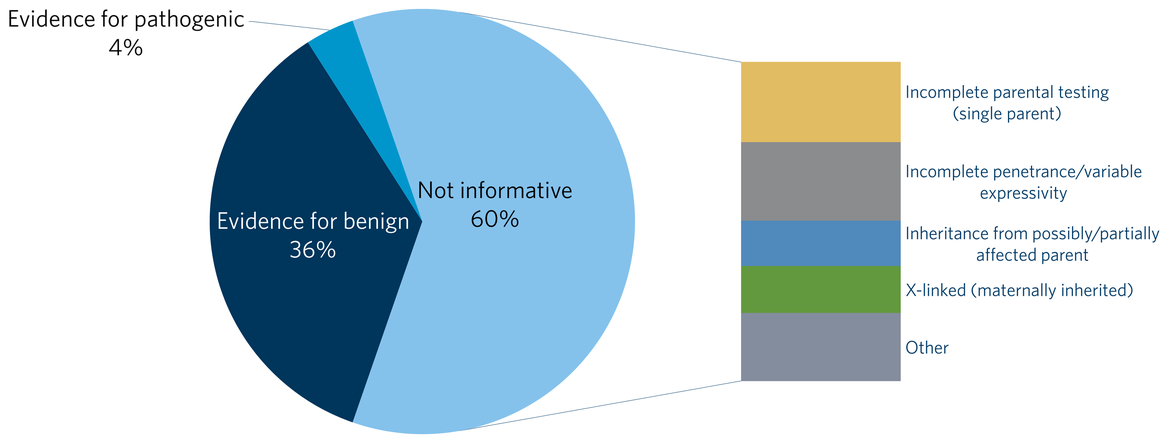
RESULTS

Cases with Parental Analysis



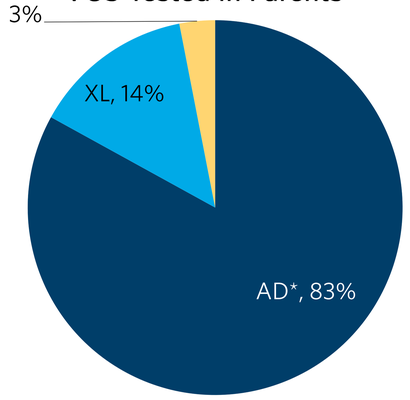
65% (230/352) cases submitted for the MGP testing had undergone parental analysis

Evidence from Parental Analysis



Parental analysis provided evidence supporting benign or pathogenic classifications in 40% of VUS (AD and XL genes)

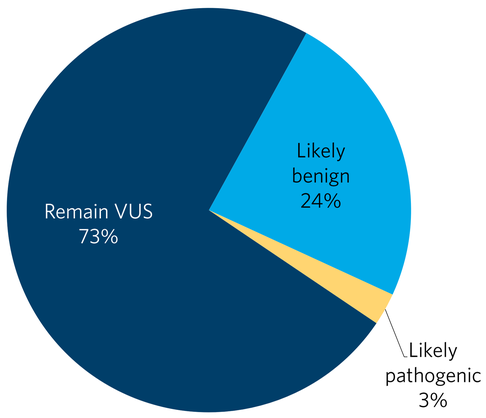
VUS Tested in Parents



A total of 359 unique VUS detected in the 230 cases were tested in available parents

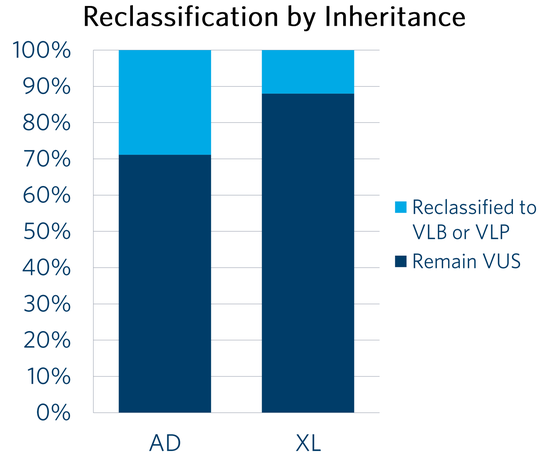
*AD includes genes that are known to have both AD and AR inheritances

Overall VUS Reclassification



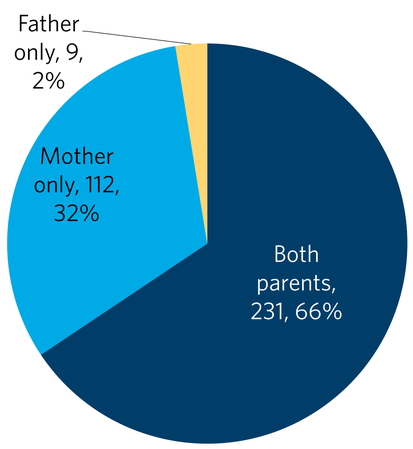
Parental analysis resulted in 27% reduction in overall VUS rate (AD and XL genes)

Reclassification by Inheritance



AD genes have increased VUS reclassification rate, compared to XL genes

Parents Available for Testing



34.4% (121/352) cases submitted for MGP testing had only single parent

De Novo and Mosaic Variants

Gene	Variant c.	Variant p.	Segregation	Reclassified	
				From	To
KCNT1	c.1429G>A	p.A477T	*De novo*	VUS	VLP
OFD1	c.655-2A>G		*De novo*	VLP	Mutation
SPTAN1	c.6908_6916dupACCAGCTGG	p.D2303_L2305dup	*De novo*	VLP	Mutation
SCN8A	c.5279T>C	p.M1760T	*De novo*	VUS	VLP
GNAO1	c.601G>T	p.D201Y	Paternal (mosaic)	VUS	VLP
GABRB3	5'UTR_3'UTRdel		*De novo*		
UBE3A	5'UTR_3'UTRdel		*De novo*		
EEF1A2	c.1084G>T	p.D362Y	*De novo*	VUS	VLP
SYNGAP1	c.3009C>G	p.S1003R	*De novo*		
SYNGAP1	EX17_3'UTRdel		*De novo*		
SIK1	c.1063C>T	p.R355C	*De novo*		
DYRK1A	c.848T>G	p.I283S	*De novo*	VUS	VLP
HCN1	c.459G>T	p.M153I	*De novo*	VUS	VLP
SCN1A	c.230T>C	p.L77P	*De novo*	VUS	VLP
GRIN2A	c.1925T>G	p.L642R	*De novo*	VUS	VLP
ARID1B	c.2605G>A	p.G869S	*De novo*		
SCN2A	c.386+2T>C		*De novo*	VLP	Mutation
PURA	c.458G>C	p.R153P	*De novo*	VUS	VLP

TAKE-HOME POINTS

- Concurrent parental analysis of VUS in highly penetrant AD and XL genes provides useful information for variant classification and reduces the overall VUS rate.
- Modes of inheritance (AD vs. XL) can have a large impact on informativeness of parental analysis.
- Incomplete parental testing (unavailability of both parents) accounts for the largest portion of uninformative analysis.
- The reduced VUS rate by upfront parental analysis can result in less complicated and more informative initial reports for patients.

REFERENCES

1. Pesaran T, et al. (2016) *Int J Breast Cancer.* 2016:2469523.

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