Ambry Genetics®

Copy Number Variation (CNV) Classification Scheme

CLARITY TO BETTER INFORM YOUR DECISIONS

Classification Minimum Threshold	Criteria
Pathogenic 1A Variant, Likely Pathogenic 3B	CNVs with ≥ 100 unique genes
	Well-established microdeletion/duplication syndromes
	CNV containing a single gene deletion (frameshift, or whole gene) with established clinical validity for autosomal dominant (AD)/X-linked (XL) disease, haploinsufficiency established as mechanism of disease
	Duplication containing a single gene with established gene-disease validity for AD/XL disease* and established triplosensitivity (TS); (the TS gene or minimal critical region is fully contained within the observed copy number gain)
	Deletions with ≥35 unique coding genes
	Duplications with ≥ 50 unique coding genes
	CNV containing a single gene deletion (frameshift, or whole gene) with established gene-disease validity for AD/XL disease, haploinsufficiency not established as mechanism of disease*
	Described in ≥5 probands, internal cases or case reports, with overlapping CNV region and overlapping clinical phenotype
	Significant disease association in one appropriately sized case-control study. OR>1.5 and p<0.05 when n>1000 case and control chromosomes across studies (Lower CI ≥1.5)
	Good segregation with disease
	Confirmed or unconfirmed *de novo* alteration
	Deletions with ≥25-49 total number of unique genes
	Duplications with ≥35-74 total number of unique genes
	Moderate segregation with disease
	CNV absent from population databases and internal database, rarity
VUS	Conflicting or insufficient evidence
Variant, Likely Benign 1D	Large case-control studies show no significant disease association
	Specific phenotype and lack of co-segregation in family study: Not identified in another affected family member with consistent, specific, well-defined phenotype
	Specific phenotype and lack of co-segregation in family study: Identified in unaffected family member and specific, well-defined phenotype observed in the proband
Benign 1F	Described in at least 1 Database of Genomic Variants (DGV) gold standard study OR 2 studies in DGV with frequency 0.5% - 0.99% of the population (n≥100)**
	Described in at least 1 DGV gold standard study OR 2 studies in DGV with frequency ≥1% of the population (n≥100)**

* If partial deletion see pathogenic criterion (PVS1) for predicted loss of function variants
** Does not apply for AR diseases
Criteria weight range: Pathogenic (1A-1C), Benign (1D-1F)

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