

Spectrum Health Copy number variant classification assertion criteria

Five basic categories:

Thought to be benign

ChAS software indicates multiple variants of the same size have been previously evaluated and determined to be benign (by population data according to Affymetrics scientific consultants). Such variants are typically small and recurrent, often attributed to low copy repeats in the region.

Genes within the variant call are not associated with any dominantly inherited phenotype (according to OMIM).

Small copy number variants within intronic regions are generally considered benign.

Likely benign

This category is employed when there are only a few similar calls in the ChAS database but there is supporting data in the Database of Genomic Variants (DGV), DECIPHER database and/or ClinVar database.

Genes within the variant call are not associated with any dominantly inherited phenotype (according to OMIM).

The copy number variant may be seen in an individual with another known disease causing variant or in a healthy presumably-normal individual.

Unclear clinical significance

Variants of unclear significance (VUSs) are those that are not clearly benign or likely benign and genes within the region are not associated with any dominantly inherited phenotype.

Similar copy number variants are generally not seen in the DGV, DECIPHER or ClinVar databases.

Parental testing is usually recommended.

Likely clinically significant

This category of copy number variants usually involves an OMIM morbid gene but the duplication or deletion is small and has not been reported as a recurrent variant of clinical significance.

Similar copy number variants are not seen in the DGV but may be listed as pathogenic or likely pathogenic in the DECIPHER or ClinVar databases.

Clinically significant

These are copy number variants known to be associated with a genetic disorder.

For deletion variants, there is confirmatory evidence in the literature of previous cases or there is supportive evidence of loss of function mutations in disease associated genes.

For duplication variants, there is evidence in the literature that copy number gain of genes in the region have been associated with a disease phenotype.

Basic references (not a comprehensive list)

Database of Genomic Variants (DGV) <http://www.dgv.tcag.ca/dgv/app/home>

DECIPHER database (includes ISCA database) <http://www.decipher.sanger.ac.uk>

ClinVar database <http://www.ncbi.nlm.nih.gov/variation/view>

OMIM (Online Mendelian Inheritance in Man) <http://www.omim.org>