ARUP Constitutional Copy Number Variant Assertion Criteria

ARUP's CNV Classification Process

Constitutional copy number variants (CNV) detected in the Genomic Microarray (GMA) Laboratory at ARUP Laboratories go through a standardized, comprehensive evaluation and classification process. This process was developed using guidance provided by the American College of Medical Genetics and Genomics (ACMG)1,2.

Resources and information utilized for CNV classification include, but are not limited to:

- Control datasets
  - Internal and platform-specific
  - Database of Genomic Variants (DGV) (includes cross-platform datasets)
  - dbVar (e.g., nstd54, nstd100 datasets)
  - Genome Aggregation Database (gnomAD)
- Clinical case datasets
  - Internal databases that capture previous constitutional cases encountered in the GMA, Cytogenetics, Genomics, or Molecular Genetics laboratories at ARUP
  - ClinVar/ClinGen
  - DECIPHER
  - dbVar (e.g., nstd54, nstd100 datasets)
- Genomic content, gene- and region-disease association resources
  - Gene prediction (e.g., NCBI RefSeq and UCSC Genes)
  - Internally curated genes and genomic regions
  - ClinGen Dosage Sensitivity Map
  - OMIM
  - HGMD
  - Peer-reviewed literature
- Clinical findings and results from other related laboratory tests
- Results from family member testing/segregation studies

ARUP’s CNV Classification Categories

ARUP’s CNV classification categories follow the standard terminology and definitions put forth by the American College of Medical Genetics and Genomics (ACMG)1:

Pathogenic: The CNV is known or expected to cause a clinical phenotype. If documented, variable expressivity and incomplete penetrance should be well understood. Examples of expected pathogenic CNVs include: 1) a large, multigenic (100’s of genes) CNV that has not yet been described in peer-reviewed literature; 2) an intragenic, multi-exonic deletion involving a known haploinsufficient gene.

Likely pathogenic: The CNV is suspected to cause a clinical phenotype however, there is only emerging/moderate evidence to support the clinical association. Examples include: 1) a moderately sized, multigenic (10’s of genes) CNV that has not yet
been described in peer-reviewed literature; 2) a CNV that has been reported in association with a specific (matching) clinical phenotype across multiple probands, but in a single publication.

Uncertain clinical significance: It is uncertain whether the CNV causes a clinical phenotype; there is insufficient evidence to support a clinical association. Examples include: 1) a smaller (1 to low 10’s of genes) CNV that has not been reported in association with clinical findings and does not represent common variation; 2) a CNV that has been reported in association with a nonspecific clinical phenotype in a single publication.

Likely benign: There is some evidence the CNV may not cause a clinical phenotype. Examples include: 1) a CNV that has been observed in control datasets, but is not known to represent a common polymorphism; 2) a CNV with no gene content that does not represent common variation.

Benign: There is sufficient evidence the CNV is not associated with clinical phenotypes. Examples include: 1) a known polymorphic CNV, occurring at >1% frequency in the general population; 2) a CNV that has been observed multiple times and has been classified, in multiple peer-reviewed publications or curated databases, as a benign variant.

Special considerations for CNVs involving recessive genes (X-linked or autosomal)

X-linked recessive: CNVs involving known X-linked recessive (XLR) genes are classified according to phenotypic expressivity in a male carrier, regardless of the sex chromosome composition of the proband. Generally, such CNVs will be classified as pathogenic.

Autosomal recessive: Consistent classification of losses involving known autosomal recessive (AR) genes is complicated by variability of CNV gene content. While a focal deletion involving a single AR gene could be easily and simply defined using the “pathogenic, autosomal recessive” classification2, in the context of whole genome testing, including GMA, the classification of a multigenic CNV is based primarily upon the potential clinical significance of the heterozygous, single-copy number state. For these reasons, ARUP utilizes a distinct autosomal recessive disease risk category for focal deletions involving a single AR gene and utilizes the 5-category system outlined above for multigenic CNVs, which include AR genes.

References