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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" classification[2], 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

1. Kearney H et al. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genet Med* 2011;13(7):680-5.
2. Richards et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24.