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ARUP CONSTITUTIONAL COPY NUMBER VARIANT ASSERTION CRITERIA

ARUP's CNV Classification Process

Constitutional copy number variants (CNVs) 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 used for CNV classification include, but are not limited to:

- Genomic content, gene- and region-disease association resources
  - Gene annotations (protein coding genes)
  - Clinical Genome Resource (ClinGen) Dosage Sensitivity and Gene-Disease Validity curations
  - HGMD
  - OMIM
  - Haploinsufficiency predictors

- Clinical case datasets
  - Internal databases
  - ClinVar
  - DECIPHER

- Control datasets
  - Database of Genomic Variants (DGV)
  - Genome Aggregation Database (gnomAD)
  - Platform-specific

- Peer-reviewed literature
- Phenotypic information and results from other related laboratory tests
- Results from familial testing

ARUP's CNV Classification Categories

ARUP's CNV classification categories follow the standard terminology and definitions put forth by the ACMG and ClinGen[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 include: 1) a CNV completely encompassing a known dosage sensitive gene or region; 2) a multigenic CNV (>35 protein-coding gene deletion or >50 protein-coding gene duplication) that has not yet been described in peer-reviewed literature and does not represent common variation.

Likely pathogenic: The CNV is suspected to cause a clinical phenotype, however the association is not yet established/ there is emerging evidence to support the association. Example: a multigenic CNV (25-34 protein-coding gene deletion or 35–49 protein-coding gene duplication) that has not yet been described in peer-reviewed literature.

Uncertain clinical significance: It is uncertain whether the CNV causes a clinical phenotype; there is insufficient or conflicting evidence to support a clinical association. Example: a smaller CNV (<25 protein-coding gene deletion or <35 protein-coding gene duplication) that has not been reported in association with clinical findings and does not represent common variation.

Likely benign: There is some evidence the CNV may not cause a clinical phenotype. Examples include: 1) a CNV that has been observed frequently in control datasets but is not known to represent a common polymorphism (<1% frequency); and 2) a CNV with no protein-coding 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; and 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) and reduced penetrance:

X-linked: CNVs involving known dosage sensitive genes on the X-chromosome 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, X-Linked. In female carriers of well-known X-linked recessive conditions where females are not typically affected, such CNVs will be classified as X-Linked Recessive Disease Risk.

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 genomic microarray testing, 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 uses a distinct autosomal recessive disease risk category for focal deletions involving a single AR gene and generally utilizes the 5-category system outlined above for multigenic CNVs which include AR genes.

Reduced penetrance: Certain recurrent CNVs classified as pathogenic or likely pathogenic are documented to exhibit reduced penetrance (generally <60%), which has been established across multiple large populations. Such CNVs will be classified using a penetrance qualifier: pathogenic or likely pathogenic, reduced penetrance, or pathogenic or likely pathogenic, low penetrance.

References

1. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med.* 2020;22(2):245-257.
2. Richards S, Aziz N, Bale S, 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;17(5):405-424.

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