ARUP LABORATORIES
A nonprofit enterprise of the University of Utah and its Department of Pathology

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ARUP Molecular Germline Variant Investigation Process

Overview

Variants detected in the clinical molecular genetics laboratories at ARUP go through a multi-faceted evaluation by a trained clinical variant scientist, followed by final review and classification by a board-certified medical director. ARUP will provide the ordering clinician with a summary of the evidence as well as an overall interpretation of the clinical significance of the detected variant(s) included on the patient's report. The variant classification process at ARUP closely follows the guidelines recommended by the American College of Medical Genetics and Genomics (ACMG).[1]

ARUP Variant Assessment Description

Variant classification is intended to assist clinicians in determining if a detected variant provides an explanation for the patient's clinical findings or whether an asymptomatic individual who inherits the variant is likely to develop the associated phenotype. To classify a variant detected in a gene known to be associated with specific phenotype(s), ARUP utilizes a comprehensive review of clinical information, data published in the medical literature, population frequency, evolutionary conservation, computational prediction programs, gene/variant databases, and other factors relevant to the gene or variant in question. ARUP utilizes the guidelines published by ACMG to classify variants detected in the laboratory and place them into the recommended five classification categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

ARUP's Modifications to ACMG Guidelines Used for Variant Classification

- Truncating variants that occur sufficiently early in a relevant transcript, in genes for which loss-of-function variants are known to be pathogenic, are generally considered pathogenic.
- Variants in certain known functional domains may be called likely pathogenic without additional data.
- Silent variants and intronic variants that are not predicted to alter splicing are called likely benign, or benign with one additional piece of supporting (BP) or strong (BS) evidence.
- Variants in autosomal dominant genes that meet BS1 with excess homozygotes in the general population databases may be called benign.
- Variants without conflicting evidence with a high population frequency (>0.1% for autosomal dominant, >1.0% for autosomal recessive) may be called likely benign without additional data. Note: this does not apply to genes with variable penetrance.
- Additional lines of evidence may be used that are disorder- or gene-specific. For more information about these specific exceptions, please contact ARUP Genetics at (800) 242-2787.
    - **Clinical Genome Resource (ClinGen):** published guidelines from ClinGen variant curation expert panels may be used for disorder- or gene-specific modifications to ACMG guidelines.
    - **Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA):** *BRCA1* and *BRCA2* variant classifications from the ENIGMA consortium expert panel may be used as supporting evidence (PP5/BP6).

- ARUP occasionally uses additional categories to describe variants that do not fit into the standard five categories of variant classification, such as:
    - **Pseudodeficiency allele:** a variant that alters the protein product in a way that affects in vitro studies (such as enzyme activity) but will not cause the associated phenotype.
    - **Risk factor:** a variant with sufficient evidence to support that it does not directly cause a phenotype, but may increase the risk of disease development.
    - **Pathogenic-mild:** a variant that is shown to result in a phenotype with reduced severity.
    - **Pathogenic-varying clinical consequences:** a variant that is shown to result in a variety of phenotypes, often ranging from severe to no phenotype.

[1.] Richards S et al. 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):405–24.

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