LABORATORY FOR MOLECULAR MEDICINE: VARIANT ASSESSEMENTS

Variant assessment is the process through which information about a novel or previously identified variant is compiled and reviewed to assign a pathogenicity classification based on established criteria. Please see our publication (Duzkale 2013; PubMed ID 24033266) for additional details on variant classification.

PRIMARY COMPONENTS:

1. ***Variant spectrum***
   - Variant spectrum for the gene is reviewed to determine if the variant type is known to be or consistent with established disease-causing variants
   - *Example:* Variant types with a strong correlation or established pathogenicity are more likely to be disease-causing
2. ***Variant frequency***
   - The frequency of each variant is estimated or determined based on presence or absence from populations of reportedly "unaffected" individuals
   - Includes NHLBI Exome Variant Server, 1000 Genomes Project, dbSNP, and other databases
   - *Example:* Variants found at higher frequencies are less likely to be disease-causing
3. ***Cases and segregation studies***
   - All cases with each variant are compiled from literature and internal data to review phenotype and presentation information
   - Family studies are reviewed to determine if a variant segregates with disease
   - *Example:* Variants occurring in multiple families and segregate with disease are more likely to be disease-causing
4. ***Functional studies***
   - In vivo/animal studies can provide supportive information
   - Data must be interpreted with care due to limitations translating study results to actual biological function

SECONDARY COMPONENTS:

1. ***Conservation/computational models***
   - Review of conservation, biochemical properties, and prediction models
   - Data must be interpreted with care since most programs have not been clinically validated
   - *Example* – Variant amino acid is present in other mammals, suggesting that this change may be tolerated
2. ***Clinical correlations***
   - Review of patient phenotype with features expected for gene
   - *Example* – An individual fulfilling Ghent criteria for Marfan syndrome supports the pathogenicity of a novel variant in *FBN1*

ASSIGNEMENT OF VARIANT CLASSIFICATION:

1. ***Evidence Review***
   - Evidence is weighted as supportive of pathogenic, neutral, or supportive of benign
   - Clinical information on current and prior cases is reconciled with available evidence
2. ***Variant Classification***
   - Variant is assigned the classification based on overall summary of weighted evidence
   - Variant classifications are reviewed and may change with additional evidence

BENIGN	LIKELY BENIGN	VARIANT OF UNCERTAIN SIGNIFICANCE	LIKELY PATHOGENIC	PATHOGENIC
- Variant frequent in the general population	- Variant seen at a low frequency in general population - Variant found in other mammals - Opposing info	- Limited or conflicting data	- Low frequency - Mod. segregation with disease - Clinical correlation - Functional evid. - De novo variant	- Strong segregation and/or functional evidence - Variant type established as disease-causing - De novo with paternity confirmed

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