

# 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*

## ASSIGNMENT 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
<ul style="list-style-type: none"> <li>- Variant frequent in the general population</li> </ul>	<ul style="list-style-type: none"> <li>- Variant seen at a low frequency in general population</li> <li>- Variant found in other mammals</li> <li>- Opposing info</li> </ul>	<ul style="list-style-type: none"> <li>- Limited or conflicting data</li> </ul>	<ul style="list-style-type: none"> <li>- Low frequency</li> <li>- Mod. segregation with disease</li> <li>- Clinical correlation</li> <li>- Functional evid.</li> <li>- De novo variant</li> </ul>	<ul style="list-style-type: none"> <li>- Strong segregation and/or functional evidence</li> <li>- Variant type established as disease-causing</li> <li>- De novo with paternity confirmed</li> </ul>