LABORATORY FOR MOLECULAR MEDICINE: VARIANT ASSESSMENTS

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

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