

# HerediLab, Inc. Laboratory Classification Definitions

HerediLab, Inc. classifies sequencing variants into one of five categories. Below is a summary of the guidelines used by our laboratory (as of 9/1/15).

## Genes known to be associated with specific phenotypes

### 1. Pathogenic

- a. Variants predicted to result in the reduced quantity or function of mature protein (may or may not have been previously reported in patients with disease)
  - i. Frameshift (an insertion or deletion that is not a multiple of 3 nucleotides)
  - ii. Nonsense (introduction of a premature stop codon)
  - iii. Splice junction (at positions +1, +2, -1, and -2 in an intron)
  - iv. Change in an initiation codon
  - v. Change in the termination codon
- b. Variants predicted to result in an amino acid replacement (missense) with one of the following conditions met:
  - i. Variant demonstration resulting in reduced protein (quantified by immunoassay)
  - ii. Common disease causing pathogenic variant based on the evidence in the literature
  - iii. Variant reported in multiple affected individuals and demonstrated to segregate with disease in multiple families
- c. Other evidence from published literature indicating pathogenicity

**Note:** For a variant to be classified as a pathogenic variant, the immunoassay, phenotype, and genotype of the patient being tested must be consistent with disease.

### 2. Likely Pathogenic (one of the three conditions must be met)

- a. Protein abnormality has been confirmed by biochemical testing
- b. Variant not present in dbSNP at a frequency consistent with being a benign variant
- c. Other evidence from published literature that indicates likelihood of pathogenicity

### 3. Benign Variant

- a. Evidence from dbSNP, ClinVar, and published literature that indicates the variant has no effect on function

\*Benign variants are interpreted as described above and not reported in clinical reports.

### 4. Likely Benign Variant (one of the following conditions must be met)

- a. Variant found is heterozygous or homozygous with a corresponding normal immunoassay
- b. Other evidence from published literature that indicates the variant has no effect on function

### 5. Variant of Unknown Clinical Significance (if unable to classify the variant in one of the four categories above, it will be classified as VOUS)

- a. Variant not reported in dbSNP or published literature
- b. Variant reported in a single individual with insufficient segregation and/or functional data
- c. Variant reported in a single individual with inadequate clinical information

**Note:** In the presence of conflicting data, the term variant of uncertain significance may be used.