MyOme's Variant Classification Process

MyOme works with an experienced external partner, Strand Life Sciences, and an internal team of PhD scientists, physicians, and genetic counselors to provide thorough variant classifications. Our approach follows the recommendations outlined by the American College of Medical Genetics (ACMG)[1], the industry standard for classifying and reporting genetic variants.

Variant Screening

Our interpretation partner first screens variants using their in-house bioinformatics tool, to help the variant interpreters prioritize variants for review. This process incorporates factors like the variant's effect on the protein, its population frequency in public databases, literature reports on pathogenicity, location in significant protein domains, experimental evidence, and the inheritance model. While this automated classification aids in prioritizing the interpreter's analysis, the interpreters further refine the evidence.

Variant Classification

Interpreters further review the selected variants in the above process by assessing technical quality, additional literature and database review, and internal variant database review. Novel variants are further assessed by in silico tools and identifying any reported variants that are close to the identified variant for known gene impacts.

The evidence collected for each variant is then weighted using the system outlined by the ACMG. Based on the criteria met, the variant is then classified into the five-tier system recommended by the ACMG (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign).

Once the external variant classification is assigned, the internal MyOme team reviews the provided evidence and logic behind the variant classification. The lab director then gives a final review and approval.

Reporting

A clinical report is generated for every patient. Variant classifications reported vary by test ordered. Proactive genetic screening panels only report on pathogenic and likely pathogenic variants, whereas diagnostic testing may also include variants of uncertain significance. The clinical report includes both a clinical summary and a summary of the evidence used for variant classification. If a variant is observed in a new case, and the last review was more than six months ago, evidence for the classification is reviewed. If new evidence is now available to support a reclassification, an amended report will be issued to the ordering provider.

Pathogenic
Sufficient evidence to support that the variant does cause disease.

Likely Pathogenic
Evidence supports the variant as being associated with disease with a greater than 90% certainty. Further scientific/clinical evidence is required to prove this conclusively.

Uncertain Significance
Insufficient evidence to classify the variant as either disease causing or benign.

Likely Benign
Evidence suggests the variant is not causative of disease with a greater than 90% certainty. Further scientific/clinical evidence is required to prove this conclusively.

Benign
Sufficient evidence to support that the variant does not cause disease.

Population Databases	gnomAD 1000 Genomes NHLBI GO Exome Sequencing Project (ESP) Internal Database dbSNP
Computational Tools	SpliceAI Pangolin REVEL CADD SIFT PolyPhen
Other Databases	ClinVar Pubmed Online Mendelian Inheritance in Man (OMIM) Human Gene Mutation Database (HGMD)

1. PMID: 25741868