



Gene-Disease Validity

Can variation in this gene cause disease?

- By reviewing genetic and experimental data in the scientific literature, ClinGen is working to identify genes in which pathogenic variants clearly cause disease.
- The gene-disease validity curation process includes 6 classification categories (below) describing the level of evidence supporting a given gene-disease relationship.
- Use this information when deciding which genes to include in clinical testing panels, and which genes require more research studies.

Definitive • Strong • Moderate • Limited • Disputed • Refuted



Dosage Sensitivity

Does loss or gain of a copy of this gene or genomic region result in disease?

- The dosage sensitivity curation process collects evidence supporting or refuting haploinsufficiency (loss) and triplosensitivity (gain) as mechanisms for disease for genes and larger genomic regions.
- Evidence is scored according to the amount of evidence available (categories below).
- Use this information when interpreting the clinical significance of variants involving loss or gain of genomic material, such as those identified by chromosomal microarray (CMA).

Sufficient Evidence • Emerging Evidence • Limited Evidence • No Evidence • Dosage Sensitivity Unlikely



Variant Pathogenicity

Which changes in the gene cause disease?

- The variant curation process combines clinical, genetic, population, and functional evidence with expert review to classify variants into 1 of 5 categories (below) according to ACMG guidelines.
- The results of these analyses are deposited in ClinVar for community access.
- Use ClinGen's variant curation tools to evaluate evidence for a variant that has not yet undergone expert review, or for classification discrepancy resolution.

Pathogenic • Likely Pathogenic • Uncertain • Likely Benign • Benign



Clinical Actionability

Are there actions that could be taken to improve outcomes for patients with this genetic risk?

- Certain genetic conditions have medical interventions that can delay symptoms, prevent disease, result in earlier detection, etc. Such conditions are considered "actionable".
- The actionability curation process evaluates availability of effective medical interventions, accounting for the chance the outcome will happen, the severity of the condition to be avoided, and the risks associated with the intervention.
- Use this information to decide which secondary finding results to report back to patients. The actionability report is not intended to inform the treatment of individual patients.

Severity and Likelihood of Disease • Efficacy and Nature of Intervention