

Variant Classification

Each variant classification is subject to professional review. Our classification system has been developed from the recommendations of the American College of Medical Genetics (ACMG) for variant classification and reporting (Richards et al. 2015).

The classification criteria for each of the five categories are as follows. A single criteria is sufficient for the classification. All classifications require that the phenotype overlaps with previous descriptions in patients with alterations in the same gene. Variants with a minor allele frequency $>0.5\%$ in case of autosomal dominant inheritance or $>2\%$ in case of autosomal recessive inheritance are considered as benign.

Pathogenic

- The variant is a predicted loss-of-function variant in a gene in which loss-of-function variants are reported to be causative.
- The variant is reported in the literature or mutation databases in multiple unrelated cases.
- The variant is rare and locus heterogeneity is absent or low and clinical diagnostics clearly hints to the alteration of a specific gene.
- Functional evidence clearly suggests a deleterious effect of the variant.

Likely Pathogenic

- The variant is reported in the literature or mutation databases in a limited number of cases, however conservation or functional predictions are suggestive of the variant causing the disease mechanism.

Variant of Unknown Significance

- Little or nothing has been reported regarding this variant or the reported evidence is incomplete and/or contradictory.

Likely benign

- The variant is reported in the literature or databases in a similar number of cases and controls.
- Variant frequency is higher than expected in the general population based on inheritance mode, disease prevalence and penetrance.
- Co-occurrence with a variant in a second gene that clearly explains the patient's phenotype.

Benign

- The variant is only reported in controls or is reported in a similar number of cases and controls.
- The variant is established in the literature as a variant that is not associated with Mendelian disease.
- Variant frequency is clearly too high to be causative based on inheritance mode, disease prevalence and penetrance.