

Counsyl Autosomal and X-linked Recessive Disease Classification criteria (2015)

Known Deleterious - KD (1 required)	A	Strong segregation with disease in multiple family members or multiple families (combined LOD \geq 3.0) AND 1 of D or E
		At least 20 alleles or >10 alleles in hemizygous male cases in X-linked recessive disorders and significant association with disease**
		>10 homozygous or compound heterozygous cases with confirmed trans configuration with another deleterious allele and significant association with disease**
		>5% of disease alleles in a well-defined population, if total # of cases is >200
		1 of F + at least 5 reported cases (compound heterozygous or homozygous cases)
		Amino acid change is the same as a Counsyl-classified KD (Exception: variants in which the mechanism of pathogenicity is altered splicing)
Likely Deleterious - LD 1 of B AND 1 of D or E OR 1 of C AND D AND at least 1 from E	B	1 of F + at least 1 reported case consistent with disease
		Significant evidence of association with disease**
	C	Suggestive segregation with disease (LOD \geq 1.5)
		Suggestive evidence of association with disease**
	D	Functional data showing deficient protein function
	E	Validated <i>in silico</i> algorithm predicts the variant to be deleterious
		Amino acid change is similar to that of an allelic KD or LD
		Allele frequency is rare in population databases
		Additional evidence of pathogenicity
	Predicted Deleterious- PD (1 required in the absence of reported cases and/or functional evidence and loss of function is a known mechanism of disease)	F
Truncating variant that results in a PTC that is located 3' of the theoretical NMD boundary + additional evidence of pathogenicity		
Initiation codon variant causing the removal of a functionally important domain or the next downstream ATG is out of frame		
Canonical splice variant AND <i>in silico</i> tools predict strong effects on splicing		
Frame shift variant that disrupts a known functional domain		

		Stop loss variant that results in significant protein elongation
Variant of Uncertain Significance - VUS (1 required)		Conflicting or insufficient evidence
Likely Benign - LB (1 required)	G	General population or subpopulation allele frequency is 1-5% (for diseases with prevalence <1/10,000 and <1/100 for X-linked)
		General population or subpopulation allele frequency > expected carrier frequency of the disease
		Internal allele frequency is 1-5% (for AR diseases with prevalence <1/10,000 and <1/100 for X-linked)
		Non-canonical intronic variant with no effects on splicing demonstrated by RT-PCR and <i>in silico tools</i> predict no effect
		Silent variant with poor conservation and no predicted or demonstrated effects on splicing
Known Benign - KB (1 required)	H	General population frequency is >5% (for AR diseases with prevalence <1/400 and <1/20 for X-linked)
		General population allele frequency > 2 x expected carrier frequency of the disease

**Specific thresholds vary by disease, depending on factors such as prevalence, the number of patients studied in the literature, and multiple hypothesis correction.

Exceptions:

- In cases of suspected patient overlap, only the most conservative case counts are used.
- Likely Deleterious classification may be downgraded to Variant of Uncertain Significance when phenotypes are mild or are not well-defined.