VARIANT CLASSIFICATION CRITERIA AND CLINICAL UTILITY

Classification	Major Criteria	Supporting Criteria	Clinical Utility
PATHOGENIC OR DISEASE-CAUSING [+ + +]	[1] Widely reported variant with conclusive evidence of a genotype-phenotype association and with consensus about its pathogenicity. [2] Demonstrated cosegregation with a phenotype (>10 meioses). [3] Cosegregation in at least 2 families (≤10 meioses), or present in at least 5 probands with the same phenotype, and meeting at least 2 supporting criteria:	A Protein-truncating variant in a gene where loss of function is a proven pathogenic mechanism. B Functional studies that support pathogenicity. C *De novo* presentation in the setting of a novel disease in the family (maternity and paternity confirmed). D Missense variant that generates the same amino-acid change as a previously reported pathogenic variant. E Variant with very low frequency/absent in the control population (MAF <0.001%).	• Clinical predictive value. • Clinical information. • Genetic counseling. • Familial screening recommended.
VERY LIKELY TO BE PATHOGENIC OR DISEASE-CAUSING [+ +]	[1] Protein-truncating variant in a gene where loss of function is a proven pathogenic mechanism that explains the patient's phenotype, and that meets at least 1 supporting criterion: [2] Missense variant/in-frame insertion or deletion in a non-repetitive region of a gene with demonstrated genotype-phenotype association that explains the patient's disease, and that meets at least 2 supporting criteria:	A Functional studies that support pathogenicity. B *De novo* presentation in the setting of a novel disease in the family (maternity and paternity confirmed). C Affecting a residue in which other pathogenic variants were previously identified. (mutational hot spot); or variant located in a relevant functional domain or region of the protein. D Variant with very low allelic frequency/absent in the control population (MAF <0.001%). E Probable cosegregation in at least one family, or various index cases, but that does not meet criteria for being considered pathogenic.	• Clinical predictive value. • Genetic counseling. (Incomplete information on penetrance and expressivity). • Familial screening recommended.
LIKELY TO BE PATHOGENIC OR DISEASE-CAUSING [+ ?]	[1]Protein-truncating variant with very low frequency/absent in the control population (MAF <0.001%) that affects a gene where loss of function is not an established pathogenic mechanism or that does not meet criteria to be considered pathogenic. [2] Intronic variant outside the consensus region of the gene for which the bioinformatics predictors agree that it would affect the splicing. [3] Missense variant/in-frame insertion or deletion in a non-repetitive region of a gene which does not meet criteria to be considered pathogenic/very likely to be pathogenic, but that meets at least 3 supporting criteria:	A Variant with very low allelic frequency/absent in the control population (MAF <0.001%). B *De novo* presentation in the setting of a novel disease in the family (maternity and paternity unconfirmed). C Patient's phenotype or family history suggests that disease could be explained by mutations in the gene (gene with well-established phenotype-genotype association). D Bioinformatics predictors agree that it would be deleterious. E Located in a mutational hot-spot, functional domain, or relevant region of the codified protein. F Reported in at least 2 unrelated individuals that presented the same phenotype.	• Currently WITHOUT clinical predictive value. • Evaluation of cosegregation can be useful to define pathogenicity.
UNKNOWN CLINICAL SIGNIFICANCE [?]	[1] Variants with contradictory information about their pathogenicity. [2] Variants that do not meet criteria for being included in another classification category.		• WITHOUT clinical predictive value. • Evaluation of cosegregation upon physicians request (research only).
UNLIKELY TO BE PATHOGENIC OR DISEASE-CAUSING [- ?]	[1] Variant allele frequency in control populations is higher than the expected for disease or has a MAF >0.05%. [2] Absence of variant cosegregation with the phenotype in at least 1 family. [3] Meeting at least 2 supporting criteria:	A Missense variant in a gene where only variants causing protein truncation have shown association with disease. B Functional study showing that the variant does not affect the structure or function of the encoded protein. C Bioinformatics predictors agree that the variant would not alter the function of the protein (including splicing variants outside the consensus region of the gene). D In-frame insertions/deletions in a repetitive gene region without a known function. E Presence of the variant in homozygosis in control population.	• WITHOUT clinical predictive value. • Familial screening NOT recommended (research only).
NON-PATHOGENIC (NOT DISEASE-CAUSING) [- -]	[1] MAF >5% in any of the control population databases. [2] Previously reported in the literature with well-established evidence of consensus about its non-disease-causing classification, and with no contradictory data. [3] Absence of cosegregation with the disease in at least 2 reported families. [4] Meeting at least 2 supporting criteria:	A Variant allele frequency in control populations is higher than expected for disease or has a MAF >0.05%. B Absence of cosegregation of the variant with the phenotype in at least 1 family. C Functional study showing that the variant does not affect the structure or function of the encoded protein. D Presence of the variant in healthy unaffected subjects at an age at which the disease should be fully penetrant (variant must be in homozygosis in recessively inherited diseases, or in hemizygosis in X-linked diseases).	• BENIGN • SHOULD NOT be included in familial screening.