Ambry Genetics®
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Ambry General Variant Classification Scheme

AMBRY CLASSIFICATION	WEIGHT	ACMG CODE	CRITERIA
Pathogenic 1A 4B 3B+2C	A	PVS1	Alterations resulting in nonsense, reading frameshift, 3' truncations, elongations, gross deletions, gross duplications, or impacting initiation codons
	B	PVS1	Canonical donor/acceptor splice sites (+/- 1, 2) or last nucleotide of exon
		PS3_RNA	Functionally-validated splicing pathogenic alteration
		PS2 & PM6	Confirmed or assumed *de novo* alteration
		PS4 or PP4	Detected in individual satisfying established diagnostic criteria for classic disease without a clear pathogenic alteration
		PM3	AR disorders, detected *in trans* with a VLP/PATH or homozygous
		PS4	Significant disease association in appropriately sized case-control study(ies)
		PP1	Good segregation with disease
		PS3	Deficient protein function in appropriate functional assay(s)
		PM5	Well-characterized pathogenic alteration at same position
		PM1	Located at a position or in a region critical for protein function
Variant, Likely Pathogenic 3B 2B+1C 1B+3C	C	PM2	Rarity in general population databases
		PP3	*In silico* model predicts deleterious
		Exome	Alteration identified in the absence of any other coding sequence pathogenic alteration ascertained in a highly unbiased cohort
VUS	Insufficient or Conflicting Evidence		
Variant, Likely Benign 1D 2E	D	BS1	Subpopulation frequency in support of benign classification
		BS2	Observed in healthy individual(s) for recessive (homozygous), dominant (heterozygous) or X-lined (hemizygous) disorders
		BS3	Intronic alteration with no splicing impact by RNA analysis
		BS3	Intact protein function observed in multiple appropriate functional assays
		BS4	Lack of segregation in affected members of a family
		BP1	Mechanism of disease is inconsistent with known cause of pathogenicity
		BP2 & BP5	Co-occurrence with VLP/PATH in same or different gene providing alternate molecular basis for disease
		BP4	Amino acid seen as reference
		no code	No disease association in appropriately sized case-control study(ies)
		BS2	Lack of phenotype in internal cohort
	E	BP3	In-frame deletions and/or insertions in a repetitive region without a known function or association with disease
		BP4	*In silico* model predicts benign
		BP7	A synonymous variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site
Benign 1F 2D 1D+2E 4E	F	BA1	General population or subpopulation frequency is too high to be pathogenic based on disease/syndrome prevalence and penetrance

The variant classification scheme is not intended for the interpretation of alterations considered epigenetic factors including genetic modifiers, multifactorial disease, or low-risk disease association alleles and may be limited in the interpretation of alterations confounded by incomplete penetrance, variable expressivity, phenocopies, triallelic or oligogenic inheritance, or skewed X-inactivation.

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One Enterprise, Aliso Viejo, CA 92656 USA Toll Free +1.866.262.7943 Fax +1.949.900.5501 ambrygen.com