Ambry Genetics®
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Ambry Genetics® General Variant Classification Scheme

Combination Rules For Classification	ACMG Code	Criteria
Pathogenic Variant 1A 4B 3B+2C Variant, Likely Pathogenic 3B 2B+2C 1B+4C	PVS1	Alterations impacting or resulting in nonsense, reading frameshift, 3' truncations, elongations, gross deletions, gross duplications, and initiation codon
	PVS1	Canonical donor/acceptor splice sites (+/- 1, 2) or Last nucleotide of exon
	PS1	Same amino acid change as VLP/P regardless of nucleotide change
	PS2 & PM6	Confirmed or assumed *de novo* alteration
	PS3	Deficient protein function in appropriate functional assay(s)
	PS3_RNA	Functionally-validated splicing variant
	PS4_PC	Detected in individual satisfying established diagnostic criteria for classic disease without a clear VLP/P and Gene-Disease Specific Proband Counting
	PS4_CC	Significant disease association in appropriately sized case-control study(ies)
	PP4	Proband specific phenotype *in vivo* functional data
	PM1	Located at a position or in a region critical for protein function
	PM2	Rarity in general population databases
	PM3	AR disorders, detected *in trans* with a VLP/P or homozygous in affected individuals
	PM4	In-frame insertions/deletions in a non-repetitive region
	PM5	Different missense variant at same amino acid position as VLP/P
	PM5_RNA	Different splicing variant at same splice site as VLP/P
	PM5_PTC	Truncating VLP/P variant downstream of the PTC
	PP1	Cosegregation with disease in affected family members
	PP2	Missense Constraint - missense variant in a region of the gene that has a low rate of benign missense variation
	PP3	*In silico* model predicts deleterious
	A_PP6	Alteration identified in the absence of any other coding sequence VLP/P ascertained in a highly unbiased cohort
VUS	Insufficient or Conflicting Evidence	
Variant, Likely Benign 1D 2E Benign Variant 1F 2D 1D+2E 4E	BA1 & BS1	General population or subpopulation frequency is too high to be pathogenic based on disease prevalence and penetrance
	BS2	Observed in unaffected individual(s) for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder
	BS3_RNA	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	Co-occurrence with VLP/P in same gene providing alternate molecular basis for disease
	BP5	Co-occurrence with VLP/P in different gene providing alternate molecular basis for disease
	BP3	In-frame insertions/deletions in a repetitive region without a known function or association with disease
	BP4_Ref	Amino acid seen as reference
	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
	A_BP8	Not predicted to impact specific critical structural or functional features
	A_BP9	No disease association in case-control study(ies)

Weight range: Pathogenic (1A-1C), Benign (1D-1F)
Codes denoted "A_" have been added as Ambry Genetics specific codes following the ACMG numbering.

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.

MKT-CORP-FLYR-10009-EN v4 | 04.07.21

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