

# Scheme For Autosomal Dominant And X-Linked Mendelian Diseases (V2-20-17)

CLASS	AMBRY CLASSIFICATION	CATEGORY	CRITERIA	EXCEPTIONS (NEW BASELINE CLASS)
5	Pathogenic Mutation	A 1 needed	Alterations resulting in premature truncation (e.g. reading frame shift, nonsense)	Truncation in close proximity to 3' terminus (3/4 gene specific) LOF has not been established as mechanism of pathogenicity (e.g. MYH7) (3)
			Other ACMG-defined mutation (i.e. initiation codon or gross deletion)	In-frame gross deletion of a single exon not in a known protein functional domain (3), Initiation codon that is not well conserved or possible alternate start (3/4), LOF has not been established as a mechanism of pathogenicity (3)
		B 4 needed	Confirmed <i>de novo</i> alteration	Weight is gene and disease specific (2B, 1B, 1C)
			Functionally validated splicing mutation	In-frame skipping of a single exon not in a known protein functional domain. LOF has not been established as a mechanism of pathogenicity. Biologically relevant, naturally occurring, in-frame isoforms with data supporting normal function (3)
			Significant disease association in appropriately sized case-control study(ies)	
			Detected in an individual satisfying established diagnostic criteria for classic disease without a clear mutation	
			Last nucleotide of exon	Last nucleotide poorly conserved or non-G, <i>in silico</i> not consistent with U2-dependent intron
			Good segregation with disease	1B=(LOD 1.5-3 = 5-9 meioses); 2 or 3B=(LOD >3 = >10 meioses) gene specific
			Deficient protein function in appropriate functional assay(s)	
			Well-characterized mutation at same position	
Other strong data supporting pathogenic classification				
4	Variant, Likely Pathogenic	3B	Alterations at the canonical donor/acceptor sites ( $\pm$ 1, 2) without other strong (B-level) evidence supporting pathogenicity	LOF has not been established as a mechanism of pathogenicity (3)
		C 4 needed	Rarity in general population databases (dbSNP, ESP, 1000 Genomes)	Dependent on disease penetrance and inheritance pattern
			<i>in silico</i> models in agreement (deleterious) and/or completely conserved position in appropriate species	<i>in silico</i> splicing predictions not used as independent line of evidence for last nucleotide of exon
			Moderate segregation with disease (at least 3 informative meioses) for rare diseases	
			Other data supporting pathogenic classification	
		3 of B		
		2 of B and at least 1 of C		
1 of B and at least 3 of C				
3	VUS	Insufficient or conflicting evidence		
		Gross duplications without strong evidence for pathogenic or benign		
2	Variant, Likely Benign	D 1 needed	Intact protein function observed in appropriate functional assay(s)	
			Intronic alteration with no splicing impact by RT-PCR analysis or other splicing assay	
			Seen <i>in trans</i> with a mutation or in homozygous state in individuals without severe disease for that gene	Genes without a defined, severe biallelic phenotype (3)
			Other strong data supporting benign classification	
		E 2 needed	Co-occurrence with mutations in the same gene (phase unknown)	Genes without a defined, severe biallelic phenotype (3) When always linked to a the same mutation (can't rule out synergetic effect)
			Co-occurrence with mutations in other highly penetrant genes that clearly explain a proband's phenotype	
			Subpopulation frequency in support of benign classification	
			<i>in silico</i> models in agreement (benign)	
			Does not segregate with disease in a family study (genes with incomplete penetrance)	
			No disease association in a small case-control study	
Other data supporting benign classification				
1	Benign	F 1 needed	General population or subpopulation frequency is too high to be a pathogenic mutation based on disease/syndrome prevalence and penetrance	
			Does not segregate with disease in a family study (genes with complete penetrance)	
			Internal frequency is too high to be a pathogenic mutation based on disease/syndrome prevalence and penetrance	
			No disease association in appropriately sized case-control study(ies)	
		1 of D and at least 2 of E		
		2 or more of D		
		>3 of E w/o conflicting data		
>4 of E w/conflicting data				

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.