ClinGen *CDH1* Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2

This version specified for the following genes: *CDH1*

Expert Panel Page: https://www.clinicalgenome.org/affiliation/50014

Release Notes/Changes from v1: **1**) PVS1 applies to initiation codon variants. **2)** Allow a variant to reach a likely benign classification based on BS1 or BS2 alone. **3)** PS3 cannot be applied if the variant meets PVS1. If the variant meets PVS1_strong, we recommend applying PS3_moderate.

ACMG/AMP Criteria Codes	Original ACMG/AMP Rule Summary	*CDH1* Rule Specifications					
		Stand Alone	**Very Strong**	**Strong**	**Moderate**	**Supporting**	**Comments**
PVS1	Null variant in a gene where LoF is a known mechanism of disease	---	Per ClinGen SVI guidelines with the exception of canonical splice sites - Apply to initiation codon variants	Per ClinGen SVI guidelines Other *CDH1* caveats: - Use the strong strength of evidence for canonical splice sites - *CDH1* Exonic deletions or tandem duplications of in-frame exons - Truncations in NMD-resistant zone located upstream the most 3' well-characterized	Per ClinGen SVI guidelines Other *CDH1* caveats: - G to non-G variants disrupting the last nucleotide of an exon - Canonical splice sites located in exons demonstrated experimentally to result in in-frame partial skipping/insertion (e.g., Exon 3 donor site)	Per ClinGen SVI guidelines	RNA analysis is recommended for splicing alterations, and if the RNA evidence does not support the prediction, the strength should be updated PP3 cannot be applied for canonical splice sites

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Related publication(s): PMID 30311375 **Date Approved: September 6, 2019**

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				pathogenic variant c.2506G>T (p.Glu836*). Use PVS1_moderate if premature stop is downstream of this variant			
PS1	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change	---	---	Per original ACMG/AMP guidelines	---	---	Variant must not impact splicing
PS2	*De novo* (both maternity and paternity confirmed) in a patient with the disease and no family history	---	≥Two patients with DGC &/or LBC w/ parental confirmation	One patient with DGC &/or LBC w/ parental confirmation	---	---	Use ClinGen's *de novo* point system for a highly specific phenotype (see Table S2)
PS3	Well-established *in vitro* or *in vivo* functional studies supportive of a damaging effect on the gene or gene product	---	---	RNA assay demonstrating abnormal out-of-frame transcripts	---	RNA assay demonstrating abnormal in-frame transcripts	This rule can only be applied to demonstrate splicing defects. PS3 cannot be applied if the variant meets PVS1. If the variant meets PVS1_strong, we recommend applying PS3_moderate.

PS4	Prevalence of variant in affected individuals is significantly increased compared to controls	---	Sixteen families meet HDGC criteria	Four families meet HDGC criteria	Two families meet HDGC criteria	One family meets HDGC criteria	This rule assumes 30% penetrance in individuals with pathogenic variants. For example, if the variant in observed in 3 families, at least one of those families need to meet criteria for HDGC in order to apply this rule. PS4 cannot be applied to variants that meet BS1 or BA1
PM1	Located in a mutational hot spot and/or critical and well-established functional domain without benign variation	---	---	---	---	---	Do not use for this gene
PM2	Absent in population databases	---	---	---	<One out of 100,000 alleles in gnomAD cohort; if present in ≥2 individuals, must be present in <One out of 50,000	---	Use gnomAD to determine allele frequency. Beware of technical limitations that can inaccurately represent allele frequency in this population database

					alleles within a sub-population		
PM3	For recessive disorders, detected in trans with a pathogenic variant	---	---	---	---	---	Does not apply to this gene
PM4	Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants	---	---	---	Per original ACMG/AMP guidelines	---	No rule specification proposed. Variant example - *CDH1* c.2647T>C (p.Ter883Glnext*29)
PM5	Novel missense change at amino acid residue where a different missense variant is pathogenic	---	---	---	---	---	Do not use rule at this time
PM6	Assumed *de novo*, but w/o confirmation of paternity and maternity	---	≥Four patients with DGC &/or LBC w/o parental confirmation	≥Two patients with DGC &/or LBC w/o parental confirmation	One patient with DGC &/or LBC w/o parental confirmation	---	Use ClinGen's *de novo* point system for a highly specific phenotype (See Table S2)
PP1	Cosegregation in multiple affected family members in a gene definitively	---	---	≥Seven meioses across ≥2 families	Five-six meioses across ≥1 families	Three-four meioses across ≥1 families	Based strength of rule code on number of meioses across one or more families

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	known to cause the disease						
PP2	Missense variant in a gene with a low rate of benign missense variation & where missense variants are a common mechanism of disease	---	---	---	---	---	Do not use rule at this time
PP3	Multiple lines of computational evidence support a deleterious effect on the gene or gene product	---	---	---	Variants affecting the same splice site as a well-characterized variant with similar or worse *in silico*/ RNA predictions	At least three *in silico* splicing predictors in agreement (.Human Splicing Finder (HSF), Maximum Entropy (MaxEnt), Berkeley Drosophilia Genome Project (BDGP), or ESEfinder)	Rule code is only for non-canonical splicing variants. Code also does not apply to last nucleotide of exon 3 (c.387G). Do not use protein-based computational prediction models for missense variants
PP4	Patient's phenotype or family history is highly	---	---	---	---	---	Use PS4 in place of PP4

	specific for a disease with a single genetic etiology						
PP5	Reputable source recently reports variant as pathogenic	---	---	---	---	---	Do not use rule at this time
BA1	Allele frequency is greater than expected for disorder	MAF cutoff of 0.2%	---	---	---	---	99.99% CI; subpopulation must have a minimum of five alleles present
BS1	Allele frequency is greater than expected for disorder	MAF cutoff of 0.1%	---	---	---	---	99.99% CI; subpopulation must have a minimum of five alleles present We allow a variant to reach a likely benign classification based on BS1 alone
BS2	Observed in a healthy adult individual for a dominant disorder with full penetrance expected at an early age	---	---	Variant seen in ≥10 individuals w/o DCG, SRC tumors, or LBC & whose families do not suggest HDGC	---	Variant seen in ≥3 individuals w/o DCG, SRC tumors, or LBC & whose families do not suggest HDGC	We allow a variant to reach a likely benign classification based on BS2 alone
BS3	Well-established *in vitro* or *in vivo* functional studies show no damaging effect	---	---	Functional RNA studies demonstrating no	---	---	This rule can only be used to demonstrate lack of splicing and can be

	on protein function or splicing			impact on transcript composition			downgraded based on quality of data
BS4	Lack of segregation in affected members of a family	---	---	Per original ACMG/AMP guidelines	---	---	Beware of the presence of phenocopies (e.g., breast cancer) that can mimic lack of segregation. Also, families may have more than one pathogenic variant contributing to another AD disorder
BP1	Missense variant in a gene for which primarily truncating variants are known to cause disease	---	---	---	---	---	Does not apply to this gene
BP2	Observed in a healthy homozygous individual, or in *trans* with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in *cis* with a pathogenic variant	---	---	Variant observed *in trans* w/known pathogenic variant (phase confirmed) **OR** observed in the homozygous state in individual w/o personal &/or family history of	---	Variant is observed *in cis* (or phase is unknown) w/ a pathogenic variant	Evidence code is dependent on strength of data. Take consideration of quality of sequencing data when applying code. Note that code requires knowledge of individuals' phenotype. Therefore, data from population databases

				DGC, LBC, or SRC tumors			should only be used when phenotypic info is available
BP3	In-frame deletions/insertions in a repetitive region without a known function	---	---	---	---	---	Do not use rule at this time
BP4	Multiple lines of computational evidence suggest no impact on gene/gene product	---	---	---	---	Splicing predictions only. At least three *in silico* splicing predictors in agreement (Human Splicing Finder (HSF), Maximum Entropy (MaxEnt), Berkeley Drosophilia Genome Project (BDGP), or ESEfinder)	This rule can only be used when splicing predictions models suggest no impact on protein. Do not use protein based computational prediction models for missense. variants
BP5	Variant found in a case with an alternate molecular basis for disease	---	---	---	---	Per original ACMG/AMP guidelines	This applies if a P/LP variant is identified in an alternate gene known to cause HDGC (e.g., *CTNNA1*)

BP6	Reputable source recently reports variant as benign	---	---	---	---	---	Do not use rule at this time
BP7	Synonymous variant which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site & the nucleotide is not highly conserved.	---	---	---	---	Synonymous variants where nucleotide is not highly conserved; variant is the reference nucleotide in one primate and/or >3 mammal species	Note the *CDH1* rule specification does not require a benign *in silico* splice prediction. This allows use with BP4, as appropriate, to classify variants meeting both criteria as likely benign