Criteria Specification

ClinGen CDH1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 3.1

Affiliation: CDH1 VCEP
Description : This version specified for the following genes: CDH1
Version : 3.1.0
Released : 3/29/2022
Release Notes :
(1) Specification of PM5_Supporting to nonsense and frameshift variants that are predicted/proved to undergo nonsense-mediated decay (NMD) or located upstream of the last known pathogenic truncating variant [c.2506G>T (p.Glu836Ter)]. (2) Column correction for PM2_Supporting from Moderate column to Supporting column.

PDF

Rules for CDH1

Gene: CDH1 (HGNC:1748)
Transcripts:
NM_004360.5

HGNC Name: cadherin 1
Disease:
hereditary diffuse gastric cancer (MONDO:0007648)

Criteria & Strength Specifications

PVS1

Original ACMG Summary

Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease.
Caveats:
• Beware of genes where LOF is not a known disease mechanism (e.g. GFAP, MYH7).
• Use caution interpreting LOF variants at the extreme 3’ end of a gene.
• Use caution with splice variants that are predicted to lead to exon skipping but leave the remainder of the protein intact.
• Use caution in the presence of multiple transcripts.

Very Strong

Per modified CDH1 PVS1 decision tree.

Strong

Per modified CDH1 PVS1 decision tree. Other CDH1 caveats:

- Use PVS1_Strong as the default strength of evidence for canonical splice site variants and follow the site-specific recommendations in the splicing table.
- CDH1 Exonic deletions or tandem duplications of in-frame exons (exon 4,5,8,9,12,13,15).

Moderate

Per modified CDH1 PVS1 decision tree. Other CDH1 caveats:

- G to non-G variants disrupting the last nucleotide of an exon.
- Canonical splice sites predicted or demonstrated experimentally to result in in-frame partial skipping/insertion (e.g., Exon 3 donor site).

Instructions: RNA analysis is recommended for splicing alterations, and if the RNA evidence does not support the prediction, the strength should be updated.

PS1

Original ACMG Summary

Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.
Example: Val->Leu caused by either G>C or G>T in the same codon.
Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level.

Not Applicable
Comments: Not applicable for CDH1.

PS2

Original ACMG Summary

De novo (both maternity and paternity confirmed) in a patient with the disease and no family history.
Note: Confirmation of paternity only is insufficient. Egg donation, surrogate motherhood, errors in embryo transfer, etc. can contribute to non-maternity.

Very Strong

≥Two patients meet the HDGC individual phenotype criteria w/ parental confirmation.

Strong

One patient meets the HDGC individual phenotype criteria w/ parental confirmation.

Instructions: Use ClinGen's de novo point system for a highly specific phenotype (see Table S2).

PS3

Original ACMG Summary

Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.
Note: Functional studies that have been validated and shown to be reproducible and robust in a clinical diagnostic laboratory setting are considered the most well-established.

Strong

RNA assay demonstrating abnormal out-of-frame transcripts.

Moderate

RNA assay demonstrating abnormal in-frame transcript.

Instructions: This rule can only be applied to demonstrate splicing defects.

PS4

Original ACMG Summary

The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls.
Note 1: Relative risk (RR) or odds ratio (OR), as obtained from case-control studies, is >5.0 and the confidence interval around the estimate of RR or OR does not include 1.0. See manuscript for detailed guidance.
Note 2: In instances of very rare variants where case-control studies may not reach statistical significance, the prior observation of the variant in multiple unrelated patients with the same phenotype, and its absence in controls, may be used as moderate level of evidence.

Very Strong

≥Sixteen families meet HDGC criteria.

Strong

Four - Fifteen families meet HDGC criteria.

Moderate

Two or three families meet HDGC criteria.

Supporting

One family meets HDGC criteria.

Instructions: Use the 2020 updated clinical practice guidelines (PMID: 32758476) as the HDGC phenotype criteria. PS4 cannot be applied to variants that meet BS1 or BA1, or to variants in which less than 30% of reported individuals meet HDGC criteria.

PM1

Original ACMG
Summary

Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation.

Not Applicable
Comments: Not applicable for CDH1.

PM2

Original ACMG
Summary

Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or Exome Aggregation Consortium.
Caveat: Population data for indels may be poorly called by next generation sequencing.

Supporting

≤ One out of 100,000 alleles in gnomAD cohort; if present in ≥2 individuals within a subpopulation, must be present in ≤ One out of 50,000 alleles.

Instructions: Use gnomAD to determine allele frequency. The mean coverage of CDH1 in the population database used should be at least 30x.

PM3

Original ACMG
Summary

For recessive disorders, detected in trans with a pathogenic variant
Note: This requires testing of parents (or offspring) to determine phase.

Not Applicable

Comments: Not applicable for CDH1.

PM4

Original ACMG Summary

Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants.

Moderate

Only apply to stop-loss variants Variant example: CDH1 c.2647T>C (p.Ter883Glnext*29).

Instructions: PM4 is not applied to small in-frame indels because the impact of amino acid level changes of CDH1 variants is inconclusive.

PM5

Original ACMG Summary

Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.
Example: Arg156His is pathogenic; now you observe Arg156Cys.
Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level.

Supporting

PM5_supporting is applicable to nonsense and frameshift variants that are predicted/proved to undergo NMD or located upstream of the last known pathogenic truncating variant. Site-specific recommendations for the application of PM5_Supporting for canonical splicing variants.

Instructions: The nonsense or frameshift variant must not impact splicing based on RNA assay or splicing predictions.

PM6

Original ACMG Summary

Assumed de novo, but without confirmation of paternity and maternity.

Very Strong

> Four patients meet the HDGC individual phenotype criteria w/o parental

confirmation.

Strong

≥Two patients meet the HDGC individual phenotype criteria w/o parental confirmation.

Moderate

One patient meets the HDGC individual phenotype criteria w/o parental confirmation

Instructions: Use ClinGen's de novo point system for a highly specific phenotype.

PP1

Original ACMG Summary

Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease.
Note: May be used as stronger evidence with increasing segregation data.

Strong

≥Seven informative meioses across ≥2 families.

Moderate

Five-six informative meioses across ≥1 family.

Supporting

Three-four informative meioses across ≥1 family.

Instructions: Based strength of rule code on number of meioses across one or more families.

PP2

Original ACMG Summary

Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.

Not Applicable

Comments: Not applicable for CDH1.

PP3

Original ACMG Summary

Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.).
Caveat: As many in silico algorithms use the same or very similar input for their predictions, each algorithm should not be counted as an independent criterion. PP3 can be used only once in any evaluation of a variant.

Moderate

Variants affecting the same splice site as a well-characterized variant with similar or worse in silico/ RNA predictions.

Supporting

At least three in silico splicing predictors in agreement (SpliceAI, MaxEntScan, SSF, GeneSplicer, HSF, TraP, varSEAK).

Instructions: PP3 cannot be applied for canonical splice sites. PP3 code also does not apply to the last nucleotide of exon 3 (c.387G). Do not use protein-based computational prediction models for missense variants.

PP4

Original ACMG Summary

Patient’s phenotype or family history is highly specific for a disease with a single genetic etiology.

Not Applicable

Comments: Not applicable for CDH1.

PP5

Original ACMG Summary

Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.

Not Applicable

This criterion is not for use as recommended by the ClinGen Sequence Variant Interpretation VCEP Review Committee. PubMed : 29543229

BA1

Original ACMG Summary

Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes or Exome Aggregation Consortium.

Stand Alone

MAF cutoff of 0.2%.

Instructions: 99.99% CI; subpopulation must ≥ 2,000 alleles and have a minimum of five variant alleles present.

BS1

Original ACMG Summary

Allele frequency is greater than expected for disorder.

Strong

MAF cutoff of 0.1%.

Instructions: 99.99% CI; subpopulation must ≥ 2,000 alleles and have a minimum of five variant alleles present. We allow a variant to reach a likely benign classification based on BS1 alone.

BS2

Original ACMG Summary

Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age.

Strong

Variant seen in ≥10 individuals w/o GC, DGC, gSRC tumors, or LBC & whose families do not suggest HDGC.

Supporting

Variant seen in ≥3 individuals w/o GC, DGC, SRC tumors, or LBC & whose families do not suggest HDGC.

Instructions: We allow a variant to reach a likely benign classification based on BS2

alone. BS2 cannot be applied to variants in which more than 30% of reported individuals meet HDGC criteria.

BS3

Original ACMG Summary

Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing.

Strong

Functional RNA studies demonstrating no impact on transcript composition.

Instructions: This rule can only be used to demonstrate lack of splicing and can only be applied to Synonymous, Intronic or Non-coding variants. BS3 may be downgraded based on quality of data.

BS4

Original ACMG Summary

Lack of segregation in affected members of a family.
Caveat: The presence of phenocopies for common phenotypes (i.e. cancer, epilepsy) can mimic lack of segregation among affected individuals. Also, families may have more than one pathogenic variant contributing to an autosomal dominant disorder, further confounding an apparent lack of segregation.

Strong

Per original ACMG/AMP guidelines.

Instructions: 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

Original ACMG Summary

Missense variant in a gene for which primarily truncating variants are known to cause disease.

Not Applicable

Comments: Not applicable for CDH1.

BP2

Original ACMG Summary

Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.

Strong

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 DGC, LBC, or SRC tumors.

Supporting

Variant is observed in cis (or phase is unknown) w/ a pathogenic variant OR observed in the homozygous state in gnomAD.

Instructions: Evidence code is dependent on the strength of data. Take consideration of the quality of sequencing data when applying code.

BP3

Original ACMG Summary

In frame-deletions/insertions in a repetitive region without a known function.

Not Applicable

Comments: Not applicable for CDH1.

BP4

Original ACMG Summary

Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc)
Caveat: As many in silico algorithms use the same or very similar input for their predictions, each algorithm cannot be counted as an independent criterion. BP4 can be used only once in any evaluation of a variant.

Supporting

Splicing predictions only. At least three in silico splicing predictors in agreement (SpliceAI, MaxEntScan, SSF, GeneSplicer, HSF, TraP, varSEAK).

Instructions: Do not use protein based computational prediction models and BP4 is not applicable for missense variants.

BP5

Original ACMG Summary

Variant found in a case with an alternate molecular basis for disease.

Supporting

Per original ACMG/AMP guidelines.

Instructions: This applies if a P/LP variant is identified in an alternate gene known to cause HDGC (currently only CTNNA1).

BP6

Original ACMG Summary

Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation.

Not Applicable

This criterion is not for use as recommended by the ClinGen Sequence Variant Interpretation VCEP Review Committee. PubMed : 29543229

BP7

Original ACMG Summary

A synonymous variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.

Supporting

Synonymous and intronic variants at or beyond +7 to -21 locations.

Instructions: Note the CDH1 rule specification does not require a conservation prediction. We allow use of BP7 with BP4, as appropriate, to classify variants meeting both criteria as likely benign.