CDH1 CanVIG-UK Gene-Specific Guidance

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CanVIG-UK review of ClinGen CDH1 VCEP v3.1 – Reviewed June 2023: Consensus to use relevant recommendations from the ClinGen CDH1 VCEP guidance (also available at: https://clinicalgenome.org/affiliation/50014/) for *CDH1* variants reported under an indication of hereditary diffuse gastric cancer. Ratified and confirmed UK use of the VCEP guidelines without changes.

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to CDH1
PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	_VSTR _STR _MOD _SUP	As per VCEP
PP4: Phenotypic specificity/case counting (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)		Not applicable as per VCEP
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_SUP	As per VCEP
PVS1: **Predicted null variant** (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD	As per VCEP
PS1: Same amino acid change as an established variant		Not applicable as per VCEP
PM4: Protein-length-changing variant	_MOD	As per VCEP

PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	_SUP	As per VCEP
PP3: In silico: *Multiple lines of computational evidence support a deleterious effect on the gene or gene product*	_MOD _SUP	As per VCEP
PM1, PP2: Enrichment/constraint: ***PP2****: Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease* ***PM1:*** *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 as per VCEP
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	_STR _MOD	As per VCEP
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease	_STR _MOD _SUP	As per VCEP
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history	_VSTR _STR _MOD	As per VCEP
PM3: in trans with a pathogenic variant (**recessive disorders)**		Not applicable as per VCEP
PP5: Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to		Not applicable as per VCEP

perform an independent evaluation		

Evidence towards Benignity

BA1/BS1: Allele frequency is "too high" in ExAC or gnomAD for disorder	_SA _STR	As per VCEP
BS2: Observation in controls inconsistent with disease penetrance. 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	_STR _SUP	As per VCEP
BP4: In silico: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)	_SUP	As per VCEP
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease		Not applicable as per VCEP
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_SUP	As per VCEP
BP3: In-frame deletions/insertions in a repetitive region		Not applicable as per VCEP
BS3: Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing	_STR	As per VCEP
BS4: Non segregation with disease	_STR	As per VCEP
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_STR _SUP	As per VCEP
BP6: Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation		Not applicable as per VCEP

BP5: Alternate molecular basis for disease	_SUP	As per VCEP

Version History/Amendments

Revised version	Date	Section	Update	Amended by	Approved by
1.0		--	Initial Version	--	