

Variant: *NM_004360.5(CDH1):c.2245C>T (p.Arg749Trp)*

CA8130235 [↗](#)

418841 (ClinVar) [↗](#)

Gene: CDH1 ([HGNC:999](#))

Condition: CDH1-related diffuse gastric and lobular breast cancer ([MONDO:0007648](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: c46e3e12-7172-498b-86a7-d9cd9f01bbee

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HGVS expressions

NM_004360.5:c.2245C>T

NM_004360.5(CDH1):c.2245C>T (p.Arg749Trp)

NC_000016.10:g.68828254C>T

CM000678.2:g.68828254C>T

NC_000016.9:g.68862157C>T

CM000678.1:g.68862157C>T

NC_000016.8:g.67419658C>T

NG_008021.1:g.95963C>T

ENST00000261769.10:c.2245C>T

ENST00000261769.9:c.2245C>T

ENST00000422392.6:c.2062C>T

ENST00000562118.1:n.463C>T

ENST00000562836.5:n.2316C>T

ENST00000566510.5:c.*911C>T

ENST00000566612.5:c.*485C>T

ENST00000611625.4:c.2308C>T

ENST00000612417.4:c.1853+1700C>T

ENST00000621016.4:c.1866-5949C>T

NM_004360.3:c.2245C>T

NM_001317184.1:c.2062C>T

NM_001317185.1:c.697C>T

NM_001317186.1:c.280C>T

NM_004360.4:c.2245C>T

NM_001317184.2:c.2062C>T

NM_001317185.2:c.697C>T

NM_001317186.2:c.280C>T

Uncertain Significance

Met criteria codes **1**

PM2_Supporting

Not Met criteria codes **25**

PS2	PS4	PS3	PS1	BA1	PP1
PP4	PP2	PP3	PM3	PM1	
PM4	PM5	PM6	BS4	BS3	
BS1	BS2	BP5	BP7	BP2	BP3
BP1	BP4	PVS1			

Expert Panel

CDH1 VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen CDH1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 3.1

[↗](#) **Criteria Specification Approval History**

Evidence submitted by expert panel

CDH1 VCEP

The NM_004360.5(CDH1):c.2245C>T (p.Arg749Trp) variant is a missense variant in exon 14 and results in the change of an Arginine to a Tryptophan. This variant is present in <1/100,000 alleles in the ExAC and gnomAD cohort (PM2_Supporting). Furthermore, it has been observed in > 10 individuals (34) without DGC, SRC tumours or LBC and whose families do not suggest HDGC. This variant has been reported in four families meeting HDGC clinical criteria, however, this represents only 11% of all families carrying this variant (threshold is 30% to consider applying PS4). Given that multiple families with this variants meet the HDGC criteria, CDH1-VCEP recommended not to apply BS2 code. In summary, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel (Variant Interpretation Guidelines Version 3.1): PM2_Supporting.

Met criteria codes

PM2_Supporting			NM_004360.5(CDH1):c.2245C>T (p.Arg749Trp) occurs at an allele frequency of 0.000003976 (1/251478) in gnomAD v2.1.1.
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Not Met criteria codes

PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			4 families meet HDGC criteria, however, this is bellow 30% of all families carrying the NM_004360.5:c.2245C>T variant. Furthermore, two carriers have LBC and one carrier has SRCC diagnosed between 50 and 60 years old.
PS3			Several original articles published by one research laboratory demonstrate the functional impact of this variant in E-cadherin expression and localization in a cancer cell line, nevertheless, further research on this subject is required.
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			Single case reported at Ambry, family did not meet HDGC criteria (Proband unknown, 2 cases breast cancer unspecified, 1 case gastric cancer unspecified)
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP3			Exceeds impact threshold in REVEL. Splicing only for CDH1.
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			This variant has been observed in 34 heterozygous individuals with no diffuse gastric cancer, signet ring cell carcinoma or lobular breast cancer and/or whose family histories do not suggest HDGC (BS2; GeneDX, Ambry, Invitae). Note that this includes five individuals with family history of unspecified gastric cancer.
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4			Exceeds impact threshold in REVEL. Splicing only for CDH1.
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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