

Variant: NM_004360.4(CDH1):c.1679C>G (p.Thr560Arg)

CA10577547 [↗](#)

234554 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 89320d2b-848b-4794-bcc3-84d990e99660

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HGVS expressions

NM_004360.4(CDH1):c.1679C>G (p.Thr560Arg)

NM_004360.4:c.1679C>G

NC_000016.10:g.68819393C>G

CM000678.2:g.68819393C>G

NC_000016.9:g.68853296C>G

CM000678.1:g.68853296C>G

NC_000016.8:g.67410797C>G

NG_008021.1:g.87102C>G

ENST00000261769.10:c.1679C>G

ENST00000261769.9:c.1679C>G

ENST00000422392.6:c.1496C>G

ENST00000562836.5:n.1750C>G

ENST00000566510.5:c.*345C>G

ENST00000566612.5:c.1566-2608C>G

ENST00000611625.4:c.1742C>G

ENST00000612417.4:c.1679C>G

ENST00000621016.4:c.1679C>G

NM_004360.3:c.1679C>G

NM_001317184.1:c.1496C>G

NM_001317185.1:c.131C>G

NM_001317186.1:c.-254-2608C>G

NM_004360.5:c.1679C>G

NM_001317184.2:c.1496C>G

NM_001317185.2:c.131C>G

NM_001317186.2:c.-254-2608C>G

NM_004360.5(CDH1):c.1679C>G (p.Thr560Arg)

Pathogenic

Met criteria codes 5

PP1_Strong

PS4

PS3

PP3

PM2_Supporting

Not Met criteria codes 21

PS2

PS1

BA1

PP4

PP2

PM4

PM3

PM1

PM5

PM6

BS3

BS4

BS1

BS2

BP5

BP7

BP3

BP2

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 c.1679C>G (p.Thr560Arg) variant is absent in the gnomAD cohort (PM2_Supporting; <http://gnomad.broadinstitute.org>). There are at least 3 in silico predictors in agreement that this variant affects splicing (PP3). There is also an RNA assay demonstrating abnormal out-of-frame transcript (PS3; PMID: 27880784). Additionally, the variant was found to co-segregation with disease in multiple affected family members, with >7 meioses observed across at least 4 families (PP1_Strong; PMID: 27880784, 29769627). This variant has been reported in at least 4 families meeting HDGC clinical criteria (PS4; PMID: 27880784, 29769627, 23709761 and SCV000580704.2). In summary, this variant meets criteria to be classified as pathogenic based on the ACMG/AMP criteria applied as specified by the CDH1 Variant Curation Expert Panel (Variant Interpretation Guidelines Version 3.1): PM2_Supporting, PP3, PS3, PP1_Strong, PS4.

Met criteria codes

PP1_Strong			Total of 8 segregations across 4 families
			Six segregations across 3 families PubMed:29769627
PS4			Four published families plus internal lab data (SCV000580704.2)
			Shows multiple family members with the CDH1 mutation and all 3 have gastric cancer PubMed:27880784
			Reports segregation in three unrelated Spanish families PubMed:29769627
			Proband with diffuse gastric cancer at age 27 PubMed:23709761
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			Predicted splicing variant. Splicing analysis shows the potential altering of splices sites through the activation of new cryptic donor and acceptor sites and the creation of an ESS site.
PM2_Supporting			Absent from controls in gnomAD

Not Met criteria codes

PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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

PP4		×	Shows multiple family members with the CDH1 mutation and all 3 have gastric cancer
PP2		×	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
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
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
BS3		×	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4		×	Six segregations across 3 families PubMed:29769627 
BS1		×	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		×	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BP3		×	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

BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	Predicted splicing variant. Splicing analysis shows the potential altering of splices sites through the activation of new cryptic donor and acceptor sites and the creation of an ESS site.
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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