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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
Approved on: 2018-11-21
Published on: 2018-12-07

HGVS expressions

NM_004360.4:c.1679C>G
NM_004360.4(CDH1):c.1679C>G (p.Thr560Arg)
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 PM2_Supporting PS4 PS3 PP3

Not Met criteria codes 21

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

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 Links 3 **Criteria Specifications for this VCEP**

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
PM2_Supporting	✔	Absent from controls in gnomAD
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.

Not Met criteria codes

PVS1	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	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	ℹ	✖	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	ℹ	✖	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.
PS2	ℹ	✖	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
PM4	ℹ	✖	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
BA1	ℹ	✖	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
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

Curation History

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