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Variant: NM_004360.4(CDH1):c.1003C>T (p.Arg335Ter)

CA166866

136055 (ClinVar)

Gene: CDH1 (HGNC:999)
Condition: CDH1-related diffuse gastric and lobular breast cancer (MONDO:0007648)
Inheritance Mode: Autosomal dominant inheritance
UUID: ce612d02-2bbe-433b-a871-e4ddcfeca78d
Approved on: 2018-11-21
Published on: 2018-12-07

HGVS expressions

NM_004360.4:c.1003C>T
NM_004360.4(CDH1):c.1003C>T (p.Arg335Ter)
NC_000016.10:g.68811854C>T
CM000678.2:g.68811854C>T
NC_000016.9:g.68845757C>T
CM000678.1:g.68845757C>T
NC_000016.8:g.67403258C>T
NG_008021.1:g.79563C>T
ENST00000261769.10:c.1003C>T
ENST00000261769.9:c.1003C>T
ENST00000422392.6:c.1003C>T
ENST00000561751.1:n.625C>T
ENST00000562836.5:n.1074C>T
ENST00000566510.5:c.847C>T
ENST00000566612.5:c.1003C>T
ENST00000611625.4:c.1003C>T
ENST00000612417.4:c.1003C>T
ENST00000621016.4:c.1003C>T
NM_004360.3:c.1003C>T
NM_001317184.1:c.1003C>T
NM_001317185.1:c.-613C>T
NM_001317186.1:c.-817C>T
NM_004360.5:c.1003C>T
NM_001317184.2:c.1003C>T
NM_001317185.2:c.-613C>T
NM_001317186.2:c.-817C>T
NM_004360.5(CDH1):c.1003C>T (p.Arg335Ter)

Pathogenic

Met criteria codes 3

PP1_Strong PVS1 PM5_Supporting

Not Met criteria codes 23

PP4 PP2 PP3 PM3 PM1 PM4 BA1 PM6 PM2 BS3 BS4 BS1 BS2 PS2 PS4 PS3

Expert Panel

CDH1 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen CDH1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 3.1*

PS1 BP5 BP7 BP2 BP3 BP1 BP4

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence Links 3

Evidence submitted by expert panel

CDH1 VCEP

The c.1003C>T (p.Arg335*) variant is predicted to result in a premature stop codon that leads to a truncated or absent protein (PVS1, PM5_Supporting). This variant was found to co-segregate with disease in multiple affected family members, with >7 meioses observed across at least two families (PP1_Strong; PMID: 16061854, 22723466, 17522512). 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): PVS1, PP1_Strong, PM5_Supporting.

Met criteria codes

PP1_Strong	✔	Variant seen in >4 families where it segregated with HDGC or LBC in >20 relatives. Proband with HDGC and Arg335X variant. Both his children and his brother and sister were all carriers and had HDGC. The proband's nephew was the only one tested who was a carrier but unaffected at the time of publication. 5 affected carriers altogether. PubMed:22723466 The Arg335X variant segregated with disease in at least 11 people from one family, with 3 others being unaffected carriers. PubMed:17522512 This variant was found in one proband with DGC who had 8 relatives with GC, 2 of which were confirmed DGC. PubMed:16061854
PVS1	✔	Nonsense variant in exon 7/16
PM5_Supporting	✔	Apply PM5_Supporting to nonsense/frameshift variants that are predicted/proved to undergo NMD.

Not Met criteria codes

PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	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
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	0.003% in GnomAD - 1 South Asian allele.
PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2		✖	0.003% in GnomAD - 1 South Asian allele.
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	Proband with HDGC and Arg335X variant. Both his children and his brother and sister were all carriers and had HDGC. The proband's nephew was the only one tested who was a carrier but unaffected at the time of publication. 5 affected carriers altogether. PubMed:22723466 The Arg335X variant segregated with disease in at least 11 people from one family, with 3 others being unaffected carriers. PubMed:17522512 This variant was found in one proband with DGC who had 8 relatives with GC, 2 of which were confirmed DGC. PubMed:16061854
BS1	ℹ	✖	0.003% in GnomAD - 1 South Asian allele.
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	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
BP5	ℹ	✖	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		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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