

Variant: NM_004360.5(CDH1):c.1703C>G (p.Thr568Arg)

Version: 1.0

CA396465435 [↗](#)

428619 (ClinVar) [↗](#)

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

Condition: CDH1-related diffuse gastric and lobular breast cancer ([MONDO:0100488](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: e931bff4-ef53-42d8-b30d-cfb0e477f7ce

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HGVS expressions

NM_004360.5:c.1703C>G

NM_004360.5(CDH1):c.1703C>G (p.Thr568Arg)

NC_000016.10:g.68819417C>G

CM000678.2:g.68819417C>G

NC_000016.9:g.68853320C>G

CM000678.1:g.68853320C>G

NC_000016.8:g.67410821C>G

NG_008021.1:g.87126C>G

ENST00000261769.10:c.1703C>G

ENST00000261769.9:c.1703C>G

ENST00000422392.6:c.1520C>G

ENST00000562836.5:n.1774C>G

ENST00000566510.5:c.*369C>G

ENST00000566612.5:c.1566-2584C>G

ENST00000611625.4:c.1766C>G

ENST00000612417.4:c.1703C>G

ENST00000621016.4:c.1703C>G

NM_004360.3:c.1703C>G

NM_001317184.1:c.1520C>G

NM_001317185.1:c.155C>G

NM_001317186.1:c.-254-2584C>G

NM_004360.4:c.1703C>G

NM_001317184.2:c.1520C>G

NM_001317185.2:c.155C>G

NM_001317186.2:c.-254-2584C>G

Likely Pathogenic

Met criteria codes 3

PM2_Supporting

PS4_Moderate

PS3

Not Met criteria codes 23

PVS1

BS2

BS1

BS4

BS3

BP4

BP3

BP1

BP2

BP5

BP7

PS1

PS2

PP1

PP2

PP3

PP4

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.1703C>G (p.Thr568Arg) missense variant is absent in the gnomAD v2.1.1 cohort (PM2_Supporting; <http://gnomad.broadinstitute.org>). This variant has been observed in two probands meeting HDGC phenotype criteria (PS4_Moderate; SCV000580691.5). RNA data indicates abnormal splicing resulting in an abnormal out-of-frame transcript (PS3, internal lab contributor). In summary, this variant meets criteria to be classified as Likely Pathogenic based on the ACMG/AMP criteria applied as specified by the CDH1 Variant Curation Expert Panel: PS3, PS4_Moderate, PM2_Supporting. (CDH1 VCEP specifications version 3.1; 03/27/2023)

Met criteria codes

PM2_Supporting			Absent in gnomAD v2.1.1
PS4_Moderate			Two probands/families meeting HDGC criteria. (Note: would like double check on Ambry Proband 2)
PS3			This rule can only be applied to demonstrate splicing defects. RNA result from reference lab indicates abnormal splicing resulting in an abnormal out-of-frame transcript.

Not Met criteria codes

PVS1			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
BS1			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			This rule can only be used to demonstrate lack of splicing and can only be applied to Synonymous, Intronic or Non-coding variants. BS3 may be downgraded based on quality of data.
BP4			Do not use protein-based computational prediction models for missense variants. Variant is not predicted to impact splicing.

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
BP2		✖	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
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	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
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3		✖	Do not use protein-based computational prediction models for missense variants. Variant is not predicted to impact splicing.
PP4		✖	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
PM1		✖	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
PM5		✖	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
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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