

Variant: *NM_004360.5(CDH1):c.489C>A (p.Cys163Ter)*

Version: 2.0

CA16620236 [↗](#)

420004 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 16aa3ae6-e72f-4623-bd36-e264690dbee1

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HGVS expressions

NM_004360.5:c.489C>A

NM_004360.5(CDH1):c.489C>A (p.Cys163Ter)

NC_000016.10:g.68808525C>A

CM000678.2:g.68808525C>A

NC_000016.9:g.68842428C>A

CM000678.1:g.68842428C>A

NC_000016.8:g.67399929C>A

NG_008021.1:g.76234C>A

ENST00000261769.10:c.489C>A

ENST00000261769.9:c.489C>A

ENST00000422392.6:c.489C>A

ENST00000561751.1:c.256C>A

ENST00000562836.5:n.560C>A

ENST00000564676.5:n.771C>A

ENST00000564745.1:n.484C>A

ENST00000566510.5:c.489C>A

ENST00000566612.5:c.489C>A

ENST00000611625.4:c.489C>A

ENST00000612417.4:c.489C>A

ENST00000621016.4:c.489C>A

NM_004360.3:c.489C>A

NM_001317184.1:c.489C>A

NM_001317185.1:c.-1127C>A

NM_001317186.1:c.-1331C>A

NM_004360.4:c.489C>A

NM_001317184.2:c.489C>A

NM_001317185.2:c.-1127C>A

NM_001317186.2:c.-1331C>A

Pathogenic

Met criteria codes **4**

PM5_Supporting

PS4_Supporting

PVS1

PM2_Supporting

Not Met criteria codes **22**

Expert Panel

CDH1 VCEP [↗](#)

Criteria Specification Information

BP5

BP7

BP4

BP3

BP1

BP2

BS1

BS4

BS3

BS2

PP1

PP2

PP3

PP4

PM6

PS1

PS2

PS3

BA1

PM1

PM3

PM4

Evidence Links 2

- [Criteria Specification: ClinGen CDH1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 3.1](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

CDH1 VCEP

The c.489C>A (p.Cys163Ter) variant is predicted to result in a premature stop codon that leads to a truncated or absent protein (PVS1, PM5_Supporting). This variant is absent in the gnomAD cohort (PM2_Supporting; <http://gnomad.broadinstitute.org>). The variant has been reported in at least one family meeting HDGC clinical criteria (PS4_Supporting; PMID 26072394). 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, PM2_Supporting, PS4_Supporting, PM5_Supporting.

Met criteria codes

PM5_Supporting			Apply PM5_Supporting to nonsense/frameshift variants that are predicted/proved to undergo NMD.
PS4_Supporting			One family that meets HDGC criteria: 2 GC cases in a family, regardless of age, at least one confirmed DGC, or personal/family history of DGC and LBC; one diagnosed <50 years (PMID: 26072394)
			One family that meets HDGC clinical criteria. Proband diagnosed with DGC, LBC, DCIS all under 50, and two first-degree relatives diagnosed with GC (1 is confirmed DGC). This is the same family reported in Kluitj et al 2012 (PMID: 22020549) PubMed:26072394 
PVS1			Creates premature termination codon in exon 4 (of 16), which is predicted to lead to loss/truncation of protein.
PM2_Supporting			Absent in gnomAD v2.1.1

Not Met criteria codes

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
BP4			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
BP2		✖	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		✖	One family that meets HDGC criteria, with the following carriers: index 'sister' affected with DGC, healthy 'sister', a healthy 'granddaughter', and her 'son' with cleft lip/palate. PubMed:22020549 
BS3		✖	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
PP1		✖	A family with no informative affected meioses (PMID: 22020549) <hr/> One family that meets HDGC criteria, with the following carriers: index 'sister' affected with DGC, healthy 'sister', a healthy 'granddaughter', and her 'son' with cleft lip/palate. PubMed:22020549 
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
PP4		✖	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
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
PS3		✖	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
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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