

Variant: *NM_004360.5(CDH1):c.715G>A (p.Gly239Arg)*

Version: 2.0

CA298980 [↗](#)

132709 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: ed68928a-1184-400b-9e8e-8f8e92950551

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HGVS expressions

NM_004360.5:c.715G>A

NM_004360.5(CDH1):c.715G>A (p.Gly239Arg)

NC_000016.10:g.68810224G>A

CM000678.2:g.68810224G>A

NC_000016.9:g.68844127G>A

CM000678.1:g.68844127G>A

NC_000016.8:g.67401628G>A

NG_008021.1:g.77933G>A

ENST00000261769.10:c.715G>A

ENST00000261769.9:c.715G>A

ENST00000422392.6:c.715G>A

ENST00000561751.1:c.454+1376G>A

ENST00000562836.5:n.786G>A

ENST00000566510.5:c.559G>A

ENST00000566612.5:c.715G>A

ENST00000611625.4:c.715G>A

ENST00000612417.4:c.715G>A

ENST00000621016.4:c.715G>A

NM_004360.3:c.715G>A

NM_001317184.1:c.715G>A

NM_001317185.1:c.-901G>A

NM_001317186.1:c.-1105G>A

NM_004360.4:c.715G>A

NM_001317184.2:c.715G>A

NM_001317185.2:c.-901G>A

NM_001317186.2:c.-1105G>A

Pathogenic

Met criteria codes 4

PM2_Supporting PS3 PS4 PP3

Not Met criteria codes 22

PVS1 BS2 BS1 BS4 BS3
BP4 BP3 BP1 BP2 BP5 BP7
PS1 PS2 PP1 PP2 PP4 BA1
PM1 PM3 PM5 PM4 PM6

Expert Panel

CDH1 VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen CDH1 Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines Version 3.1

Evidence submitted by expert panel

CDH1 VCEP

The c.715G>A (p.Gly239Arg) variant is absent in the gnomAD cohort (PM2_supporting; <http://gnomad.broadinstitute.org>). This variant has been reported in at least 16 families (18) meeting HDGC clinical criteria (PS4_very strong; PMID: 17545690, 23264079, 23264079, 26182300; SCV000153869.9, SCV000273881.6, internal laboratory contributors). This variant is predicted to affect splicing by at least 3 in silico splicing predictors in agreement (PP3). There are RNA assays demonstrating an abnormal out-of-frame transcript for this variant (PS3; PMID: 17545690, 33619332). 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 (v3.1): PS4_very strong, PS3, PM2_supporting, PP3.

Met criteria codes

PM2_Supporting			Absent in gnomAD 2.1.1 and 3.1.
PS3			PMID: 17545690 - RNA studies (patient RNA and minigene assays) have detected an abnormal out of frame transcript with the first 29 base pairs of exon 6 deleted in individuals with this alteration. PMID: 33619332 - Deletion of 29 nucleotides from the 5' end of exon 6 was seen in 54% of analysed clones. CDH1 r.906g>a (c.715A) transcript may result in full-length product with the mutant “A” transcript at CDH1 c.715 position in about 1% of the transcripts. PMID: 17221870 - Protein studies show that this variant confers deficient E-cadherin function with respect to intercellular adhesion and suppression of invasion in vitro. PMID: 19268661 - increased motility with reduced affinity for EGFR and higher EGFR activation.
PS4			18 probands/families meet HDGC phenotype criteria and very strong evidence level of PS4 is applied. PMID: 17545690 - 4 cases of gastric cancer (1 diffuse) in one family - meets HDGC criteria. PMID: 17221870 - one proband with DGC at 30 years, mother died of DGC 29 years old - meets HDGC criteria. PMID: 23264079 - 28-year-old male with diffuse gastric cancer - meets HDGC criteria. PMID: 26182300 - DGC at 31 years old - meets HDGC criteria. PMID: 16924464 - reported as HDGC, but no clinical details. PMID: 26845104 - gastric cancer, but no pathology. PMID: 28873162 - advanced cancer, but no pathology. PMID: 26681312 - breast cancer, but no pathology. SCV000153869.9 (Invitae) - 5 families meet criteria. SCV000273881.6 (Ambry) - one family meets criteria. GeneDx - none meets criteria. NCI - 8 families meet criteria.
PP3			SpliceAI: Acceptor Gain - score = 0.97 at 2 bp downstream of the variant. Acceptor Loss - score = 0.11 at -27 bp. Donor Loss - score = 0.07 at 38 bp. SSF, MaxENT and NNSplice - predict that the variant creates a 3' acceptor site (at c.717) without a significant impact on the canonical splice site.

Not Met criteria codes

PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			SCV000210903.14 (Genedx) - 3 families (there is breast cancer in every family, no gastric). SCV000153869.9 (Invitae) - 3 families (breast cancer, no gastric). Ambry - 2 families (no gastric) BS2 cannot be applied to variants in

which more than 30% of reported individuals meet HDGC criteria.

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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			VarSEAK: Class 1, No splicing effect.
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
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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Showing 1 to 3 of 3 rows		
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