

Variant: NM_004360.4(CDH1):c.8C>G (p.Pro3Arg)

Version: 3.0

CA294410 [↗](#)

142469 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e8086e46-6b34-49be-97a3-19ddcfa1b1db

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HGVS expressions

NM_004360.4:c.8C>G

NM_004360.4(CDH1):c.8C>G (p.Pro3Arg)

NC_000016.10:g.68737423C>G

CM000678.2:g.68737423C>G

NC_000016.9:g.68771326C>G

CM000678.1:g.68771326C>G

NC_000016.8:g.67328827C>G

NG_008021.1:g.5132C>G

ENST00000261769.10:c.8C>G

ENST00000261769.9:c.8C>G

ENST00000422392.6:c.8C>G

ENST00000566510.5:c.8C>G

ENST00000566612.5:c.8C>G

ENST00000611625.4:c.8C>G

ENST00000612417.4:c.8C>G

ENST00000621016.4:c.8C>G

NM_004360.3:c.8C>G

NM_001317184.1:c.8C>G

NM_001317185.1:c.-1608C>G

NM_001317186.1:c.-1812C>G

NM_004360.5:c.8C>G

NM_001317184.2:c.8C>G

NM_001317185.2:c.-1608C>G

NM_001317186.2:c.-1812C>G

Likely Benign

Met criteria codes **1**

BS2

Not Met criteria codes **25**

BA1	BS1	BS4	BS3	BP5	BP7
BP4	BP3	BP1	BP2	PVS1	
PS1	PS2	PS3	PS4	PP1	PP2
PP3	PP4	PM1	PM3	PM5	
PM4	PM6	PM2			

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**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

CDH1 VCEP

The c.8C>G (p.Pro3Arg) variant has an allele frequency of 0.00025 (39/155276) in gnomAD and is observed in multiple subpopulations, with a maximum frequency of 0.00072 (7/9712) in the European (Finnish) subpopulation (<http://gnomad.broadinstitute.org>). This variant was observed more than 70 probands without a personal history of DGC, SRC tumours or LBC and whose families do not meet HDGC clinical criteria (BS2; SCV000210891.12, SCV000186617.6). The variant has also been identified in at least 5 individuals with LBC but whose families do not meet HDGC clinical criteria (PMID: 20921021, SCV000210891.12). This variant is located in the signal peptide of the E-cadherin pre-protein and would be predicted to impact membrane localization. However, localization to the plasma membrane was not affected when the variant was expressed in cells lacking endogenous expression of E-cadherin (PMID: 20921021). In summary, the clinical significance of this variant is classified as likely benign based on BS2 alone. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel (Variant Interpretation Guidelines Version 3.1): BS2.

Met criteria codes

BS2			This variant has been observed in 22 probands without a personal history of DGC, SRC tumours or LBC and whose families do not meet HDGC clinical criteria (SCV000210891.12). The variant has been observed in an additional 63 individuals, 51 of whom have clinical data available (SCV000186617.6).
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Not Met criteria codes

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant has an allele frequency of 0.00025 (39/155276) in gnomAD and 0.00009 in ExAC (1/10836). In gnomAD, the allele is observed in multiple subpopulations and has a maximum frequency of 0.00072 (7/9712) in the European (Finnish) subpopulation.
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			This variant is located in the signal peptide of the E-cadherin pre-protein and would be predicted to impact membrane localization. Localization to the plasma membrane was not affected when this variant was expressed in cells lacking endogenous expression E-cadherin (PMID: 20921021). This variant is located in the signal peptide of the E-cadherin pre-protein and would be predicted to impact membrane localization. Localization to the plasma membrane was not affected when this variant was expressed in cells lacking endogenous expression E-cadherin. PubMed:20921021 
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP7			Not applicable.
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			Not applicable.
BP1			Not applicable.
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			Not applicable.
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			This variant is located in the signal peptide of the E-cadherin pre-protein and would be predicted to impact membrane localization. Localization to the plasma membrane was not affected when this variant was expressed in cells lacking endogenous expression E-cadherin. PubMed:20921021 
PS4			This variant was identified in an individual with LBC at 38 years and family history of breast cancer (PMID: 20921021). This variant has also been identified in four individuals with LBC but whose families did not meet HDGC clinical criteria. This variant was identified in an individual with lobular breast cancer at 38 years and family history of breast cancer. PubMed:20921021 
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			Not applicable.
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			Not applicable.
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM3		✖	Not applicable.
PM5		✖	Not applicable.
PM4		✖	Not applicable.
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
		
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