

Variant: *NM_004360.4(CDH1):c.1137+1G>A*

Version: 2.0

[CA10580104](#)

[233979 \(ClinVar\)](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 8ce34bc3-a1c5-4a8f-b0a7-bacacf8a921a

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HGVS expressions

NM_004360.4:c.1137+1G>A

NM_004360.4(CDH1):c.1137+1G>A
NC_000016.10:g.68812264G>A
CM000678.2:g.68812264G>A
NC_000016.9:g.68846167G>A
CM000678.1:g.68846167G>A
NC_000016.8:g.67403668G>A
NG_008021.1:g.79973G>A
ENST00000261769.10:c.1137+1G>A
ENST00000261769.9:c.1137+1G>A
ENST00000422392.6:c.1137+1G>A
ENST00000562836.5:n.1208+1G>A
ENST00000565810.1:n.181+1G>A
ENST00000566510.5:c.981+1G>A
ENST00000566612.5:c.1137+1G>A
ENST00000611625.4:c.1137+1G>A
ENST00000612417.4:c.1137+1G>A
ENST00000621016.4:c.1137+1G>A
NM_004360.3:c.1137+1G>A
NM_001317184.1:c.1137+1G>A
NM_001317185.1:c.-479+1G>A
NM_001317186.1:c.-683+1G>A
NM_004360.5:c.1137+1G>A
NM_001317184.2:c.1137+1G>A
NM_001317185.2:c.-479+1G>A
NM_001317186.2:c.-683+1G>A

Likely Pathogenic

Met criteria codes 4

PVS1_Strong **PP1** **PM5_Supporting**
PS4_Moderate

Not Met criteria codes 22

BP4 **BP3** **BP1** **BP2** **BP5** **BP7**
PS1 **PS2** **PS3** **PP2** **PP3** **PP4**

Expert Panel

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 Links 9

Evidence submitted by expert panel

CDH1 VCEP

The c.1137+1G>A variant is a canonical splice variant predicted to result in a truncated or absent protein (PVS1_Strong, PM5_Supporting). This variant is present in <1/100,000 alleles in the gnomAD cohort, however it is present in >1/50,000 alleles in the African sub-population (<http://gnomad.broadinstitute.org>). This variant was found to co-segregate with disease in multiple affected family members, with 3 meioses observed in one family (PP1; PMID: 10477433). This variant has also been reported in at least two families meeting HDGC clinical criteria (PS4_Moderate; PMID: 28195815, 10477433). 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 (Variant Interpretation Guidelines Version 3.1): PVS1_Strong, PS4_Moderate, PM5_Supporting and PP1.

Met criteria codes

- | | | |
|-----------------------|---|--|
| PVS1_Strong |   | Canonical +1 donor splice site variant in intron 8 predicted to result in a truncated or absent protein |
| PP1 |   | Co-segregates with diffuse gastric cancer over 3 meioses in one family that fulfils the clinical HDGC criteria (PMID: 10477433). |
| | | Co-segregates with diffuse gastric cancer over 3 meioses PubMed:10477433  |
| PM5_Supporting |   | Apply PM5_Supporting to the variant with the alteration at canonical splicing site. |
| PS4_Moderate |   | Two families meeting HDGC clinical criteria (PMID: 28195815, 10477433). Two unrelated probands do not meeting HDGC criteria (SCV000568305.3). One proband pathology unknown (SCV000278454.5). Seven unrelated probands do not meet HDGC criteria (SCV000288420.3). |

Review article [PubMed:12647996](#) 

Review article [PubMed:11665720](#) 

Review article [PubMed:20373070](#) 

Review article [PubMed:16997156](#) 

Unaffected proband age unknown with a family history of ovarian cancer [PubMed:30264118](#) 

Review article [PubMed:20233471](#) 
























One family meeting HDGC clinical criteria [PubMed:10477433](#) 















Proband age 35 years with multifocal, high-grade invasive adenocarcinoma, of signet-ring cell/diffuse type. Breast with atypical lobular hyperplasia and lobular carcinoma in situ with no evidence of malignancy.


[PubMed:28195815](#) 

Review article [PubMed:19725995](#) 

Not Met criteria codes

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
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
PS3			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
PP4			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

PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			Variant is present in gnomAD at <1/100,000 alleles (2/277,198 total). However, it is >1/50,000 alleles in the African sub-population (2/24,028). Thus, criterion is not met.
BA1			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			Co-segregates with diffuse gastric cancer over 3 meioses PubMed:10477433 
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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