

Variant: NM_004360.4(CDH1):c.1008G>T (p.Glu336Asp)

CA280990 [↗](#)

18453 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f17d1590-599b-49d7-a1e0-273ed56fef12

Approved on: 2018-11-21

Published on: 2018-12-07

HGVS expressions

NM_004360.4:c.1008G>T

NM_004360.4(CDH1):c.1008G>T (p.Glu336Asp)

NC_000016.10:g.68811859G>T

CM000678.2:g.68811859G>T

NC_000016.9:g.68845762G>T

CM000678.1:g.68845762G>T

NC_000016.8:g.67403263G>T

NG_008021.1:g.79568G>T

ENST00000261769.10:c.1008G>T

ENST00000261769.9:c.1008G>T

ENST00000422392.6:c.1008G>T

ENST00000561751.1:c.630G>T

ENST00000562836.5:n.1079G>T

ENST00000566510.5:c.852G>T

ENST00000566612.5:c.1008G>T

ENST00000611625.4:c.1008G>T

ENST00000612417.4:c.1008G>T

ENST00000621016.4:c.1008G>T

NM_004360.3:c.1008G>T

NM_001317184.1:c.1008G>T

NM_001317185.1:c.-608G>T

NM_001317186.1:c.-812G>T

NM_004360.5:c.1008G>T

NM_001317184.2:c.1008G>T

NM_001317185.2:c.-608G>T

NM_001317186.2:c.-812G>T

Likely Pathogenic

Met criteria codes 4

PVS1_Moderate

PS3

PS4_Moderate

PM2_Supporting

Not Met criteria codes 22

PM6

PM3

PM4

PM5

PM1

BS4

BS3

BS1

BS2

PS2

PS1

BP5

BP7

BP2

BP3

BP1

BP4

BA1

PP4

PP1

PP2

PP3

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.1008G>T (p.Glu336Asp) variant results in a G to non-G change at the last nucleotide of an exon (PVS1_Moderate). This variant is absent in the gnomAD cohort (PM2_Supporting; <http://gnomad.broadinstitute.org>). There is an RNA assay demonstrating an abnormal out-of-frame transcript for this variant (PS3; PMID: 9537325). Additionally, the variant has also been reported in at least two families meeting HDGC clinical criteria (PS4_Moderate; PMID: 9537325 and internal laboratory data). 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_Moderate, PM2_Supporting, PS3, PS4_Moderate.

Met criteria codes

PVS1_Moderate			G to non-G variants disrupting the last nucleotide of an exon.
PS3			PMID: 9537325- RT-PCR and sequencing shows activation of a cryptic splice site. Results in inclusion of 7bp from the intron. Will create an early STOP in exon 8. RNA sequencing demonstrated this variant results in a 7-bp insertion (r.1007_1008insTGTCAGG, p.(Glu336Aspfs*16)) in a major transcript, with other minor transcripts showing frameshifts detected (internal data).
PS4_Moderate			Two families meeting IGCLC criteria, including the original Maori family reported by Guilford et al. (PMID: 9537325) and in a proband with bilateral LBC and FHx of unspecified gastric, breast, and abdominal cancers (internal data).
Multiple generation family with HDGC and variant. PubMed:9537325 			
PM2_Supporting			Based on ExAC, 1000 Genomes, or ESP.

Not Met criteria codes

PM6			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
PM5			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
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	PMID: 9537325- RT-PCR and sequencing shows activation of a cryptic splice site. Results in inclusion of 7bp from the intron. Will create an early STOP in exon 8.
BS1		✖	Based on ExAC, 1000 Genomes, or ESP.
BS2		✖	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
PS1		✖	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
BP2		✖	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
BP4		✖	Splice predictors - all three predict loss of splice site; using PVS1_moderate instead
BA1		✖	Based on ExAC, 1000 Genomes, or ESP.
PP4		✖	PMID: 9537325 1 family with DGC. Family in spreadsheet does not have details on GC being DGC, will not count.
PP1		✖	One big family, multiple generations affected with DGC. Linkage analysis points to CDH1 gene, haplotype analysis shows it is found in affected, obligate carriers and some unaffected. Variant genotyped in 2 affected and 4 obligate carriers.

PP2		No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	 	Splice predictors - all three predict loss of splice site; using PVS1_moderate instead

Curation History 	
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