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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(CDH1):c.1008G>T (p.Glu336Asp)
NM_004360.4:c.1008G>T
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 PS4_Moderate PS3 PM2_Supporting

Not Met criteria codes 22

PM3 PM4 PM5 PM1 PM6 BA1 BS2 BS4 BS3 BS1 BP2 BP3 BP1 BP4 BP5 BP7 PS2 PS1 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 Links 1 **Criteria Specifications for this VCEP**

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.
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
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).
PM2_Supporting	✔	Based on ExAC, 1000 Genomes, or ESP.

Not Met criteria codes

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

PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	Based on ExAC, 1000 Genomes, or ESP.
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	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	ℹ	✖	Based on ExAC, 1000 Genomes, or ESP.
BP2	ℹ	✖	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	ℹ	✖	Splice predictors - all three predict loss of splice site; using PVS1_moderate instead
BP5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	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
PP4		✖	PMID: 9537325 1 family with DGC. Family in spreadsheet does not have details on GC being DGC, will not count.
PP1	ℹ	✖	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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