

Variant: *NM_004360.5(CDH1):c.1057G>A (p.Glu353Lys)*

Version: 2.0

CA10577540 [↗](#)

234571 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 60a7410c-1a25-4d28-8b31-90b524be8a48

Approved on: 2023/8/24

Published on: 2023/8/24

HGVS expressions

NM_004360.5:c.1057G>A

NM_004360.5(CDH1):c.1057G>A (p.Glu353Lys)

NC_000016.10:g.68812183G>A

CM000678.2:g.68812183G>A

NC_000016.9:g.68846086G>A

CM000678.1:g.68846086G>A

NC_000016.8:g.67403587G>A

NG_008021.1:g.79892G>A

ENST00000261769.10:c.1057G>A

ENST00000261769.9:c.1057G>A

ENST00000422392.6:c.1057G>A

ENST00000561751.1:c.679G>A

ENST00000562836.5:n.1128G>A

ENST00000565810.1:n.101G>A

ENST00000566510.5:c.901G>A

ENST00000566612.5:c.1057G>A

ENST00000611625.4:c.1057G>A

ENST00000612417.4:c.1057G>A

ENST00000621016.4:c.1057G>A

NM_004360.3:c.1057G>A

NM_001317184.1:c.1057G>A

NM_001317185.1:c.-559G>A

NM_001317186.1:c.-763G>A

NM_004360.4:c.1057G>A

NM_001317184.2:c.1057G>A

NM_001317185.2:c.-559G>A

NM_001317186.2:c.-763G>A

Likely Pathogenic

Met criteria codes **4**

PS4_Moderate

PP3

PS3

PM2_Supporting

Not Met criteria codes **21**

PVS1

BA1

BP5

BP7

BP4

BP3

BP1

BS1

BS4

BS3

BS2

Expert Panel

CDH1 VCEP [↗](#)

Criteria Specification Information

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

Evidence submitted by expert panel

CDH1 VCEP

The c.1057G>A (p.Glu353Lys) variant is absent in the gnomAD cohort (PM2_supporting; <http://gnomad.broadinstitute.org>). This variant has been reported in at least two families meeting HDGC clinical criteria (PS4_moderate; SCV001378233.1, SCV000580696.4). There is an RNA assay demonstrating an abnormal out-of-frame transcript for this variant (PS3; PMID: 32133419). This variant is predicted to affect splicing by SpliceAI (Donor Gain: score = 0.54 at -3 bp) (PP3). 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 (v3.1): PS3, PS4_moderate, PM2_supporting, PP3.

Met criteria codes

PS4_Moderate			SCV001378233.1 (Invitae) - 1 family meets criteria (proband GIST but father signet cell gastric adenocarcinoma in 30s) SCV000580696.4 (Ambry) - 1 family meets criteria (3 cases stomach, including 1 diffuse in 20s)
PP3			SpliceAI - Donor Gain: score = 0.54 at -3 bp (upstream of the variant), c.1055. SSF = 90.31->94.67 (+4.8%). MaxENT = 9.16->10.51 (+14.8%). NNSPLICE = 0.99->1.00 (+0.8%).
PS3			PMID: 32133419 - RNA studies demonstrate abnormal splicing in the set of samples tested (Ambry internal data) - CDH1 r.1055_1137del (out-of-frame).
			RNA studies demonstrate abnormal splicing, r.1055_1137del (out-of-frame). PubMed:32133419 
PM2_Supporting			Absent in gnomAD 2.1.1 and 3.1.

Not Met criteria codes

PVS1			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
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

BP4			VarSEAK: 5' DONOR SPLICE SITE PREDICTION - Likely 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
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
BS2			GeneDx - 1 family (some with breast cancer). Invitae - 1 family (breast, no gastric). Ambry - 1 family (breast, no gastric). BS2 cannot be applied to variants in which more than 30% of reported individuals meet HDGC criteria.
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
PM6			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

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

Curation History 		
		<div></div> <div>▼</div> <div>▼</div>
Showing 1 to 2 of 2 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.