

Variant: *NM_004360.5(CDH1):c.2474dup (p.Pro826fs)*

Version: 1.0

CA658658499 [↗](#)

481178 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: d92ac761-791e-4dbf-a19a-d7fd110fd456

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HGVS expressions

NM_004360.5:c.2474dup

NM_004360.5(CDH1):c.2474dup (p.Pro826fs)

NC_000016.10:g.68833324dup

CM000678.2:g.68833324dup

NC_000016.9:g.68867227dup

CM000678.1:g.68867227dup

NC_000016.8:g.67424728dup

NG_008021.1:g.101033dup

ENST00000261769.10:c.2474dup

ENST00000261769.9:c.2474dup

ENST00000422392.6:c.2291dup

ENST00000562118.1:n.692dup

ENST00000562836.5:n.2545dup

ENST00000566510.5:c.*1140dup

ENST00000566612.5:c.*714dup

ENST00000611625.4:c.2537dup

ENST00000612417.4:c.1854-867dup

ENST00000621016.4:c.1866-879dup

NM_004360.3:c.2474dup

NM_001317184.1:c.2291dup

NM_001317185.1:c.926dup

NM_001317186.1:c.509dup

NM_004360.4:c.2474dup

NM_001317184.2:c.2291dup

NM_001317185.2:c.926dup

NM_001317186.2:c.509dup

Pathogenic

Met criteria codes 4

PVS1_Strong

PM5_Supporting

PS4

PM2_Supporting

Not Met criteria codes 22

BA1

BS1

BS4

BS3

BS2

BP5

BP7

BP4

BP3

BP1

BP2

PS1

Expert Panel

CDH1 VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

CDH1 VCEP

The NM_004360.5:c.2474dup (p.Pro826AlafsTer3) variant in CDH1 is a frameshift variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay. However, this truncated region (removes last 57 amino acids of the protein) is critical to protein function and located upstream the most 3' well-characterized pathogenic variant c.2506G>T (pGlu836Ter) (PVS1_Strong, PM5_Supporting; PMID: 29798843, ClinVar Variation ID: 479504). This variant is absent in gnomAD 2.1.1 (PM2_Supporting). This variant has been reported in 5 families meeting HDGC criteria (PS4; NCI hereditary gastric study, Ambry, Invitae). In summary, this variant meets the criteria to be classified as pathogenic for DGLBCS based on the ACMG/AMP criteria applied, as specified by the ClinGen CDH1 VCEP: PVS1_Strong, PS4, PM2_Supporting, PM5_Supporting. (CDH1 VCEP specifications version 3.1; 5/6/2022)

Met criteria codes

PVS1_Strong			The NM_004360.5:c.2474dup (p.Pro826AlafsTer3) variant in CDH1 is a frameshift variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay. However, this truncated region (removes last 57 amino acids of the protein) is critical to protein function and located upstream the most 3' well-characterized pathogenic variant c.2506G>T (pGlu836Ter) (PVS1_Strong; PMID: 29798843).
PM5_Supporting			This variant is located upstream of last known pathogenic truncating variant [c.2506G>T (p.Glu836Ter)] [PMID: 29798843, ClinVar Variation ID: 479504](PM5_Supporting).
PS4			This variant has been reported in 5 families meeting HDGC criteria (PS4; NCI hereditary gastric study, Ambry, Invitae).
PM2_Supporting			This variant is absent in gnomAD 2.1.1 (PM2_Supporting).

Not Met criteria codes

BA1			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			Observed in one unaffected female in her 30s. Family history of breast cancer (NOS) in the proband's mother (dx 40s).
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			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
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
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
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

