

Variant: *NM_004360.4(CDH1):c.2386dup (p.Arg796Profs)*

Version: 2.2

CA723143791 [↗](#)

12236 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 690b78a0-7ef7-4105-9b06-180bff60cf0c

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HGVS expressions

NM_004360.4(CDH1):c.2386dup (p.Arg796Profs)

NM_004360.4:c.2386dup

NC_000016.10:g.68829744dup

CM000678.2:g.68829744dup

NC_000016.9:g.68863647dup

CM000678.1:g.68863647dup

NC_000016.8:g.67421148dup

NG_008021.1:g.97453dup

ENST00000261769.10:c.2386dup

ENST00000261769.9:c.2386dup

ENST00000422392.6:c.2203dup

ENST00000562118.1:n.604dup

ENST00000562836.5:n.2457dup

ENST00000566510.5:c.*1052dup

ENST00000566612.5:c.*626dup

ENST00000611625.4:c.2449dup

ENST00000612417.4:c.1853+3190dup

ENST00000621016.4:c.1866-4459dup

NM_004360.3:c.2386dup

NM_001317184.1:c.2203dup

NM_001317185.1:c.838dup

NM_001317186.1:c.421dup

NM_004360.5:c.2386dup

NM_001317184.2:c.2203dup

NM_001317185.2:c.838dup

NM_001317186.2:c.421dup

Likely Pathogenic

Met criteria codes 3

PM2_Supporting

PVS1_Strong

PS4_Supporting

Not Met criteria codes 23

PS1

PS2

PS3

BA1

PP1

PP2

PP3

PP4

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS3

Expert Panel

CDH1 VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen CDH1 Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines Version 3.1

Evidence Links1

Evidence submitted by expert panel

CDH1 VCEP

The c.2265T>A p.(Arg796Profs*11) variant is predicted to result in a premature stop codon that leads to a truncated protein (disrupting the last 87 amino acid residues of the CDH1 protein), and is located within the nonsense-mediated decay resistance region (downstream of aa 795) upstream of c.2506G>T p.(Glu836*) variant (PVS1_strong). This variant has been reported in at least one family meeting HDGC clinical criteria (PS4_Supporting; PMID: 9537325). The variant is absent in the gnomAD cohort (PM2_Supporting; <http://gnomad.broadinstitute.org>). 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, PM2_Supporting, PS4_Supporting.

Met criteria codes

PM2_Supporting			Not observed in population database.
PVS1_Strong			Amino acid 795 is the last aa for invoking PVS1, because anything downstream is predicted to escape NMD. This variant is upstream of the most 3' pathogenic variant, which is c.2506G>T p.(Glu836*), therefore PVS1_strong is invoked. Other downstream truncating variants are: c.2398delC (p.Arg800Alafs) - pathogenic (ClinGen EP) - CDH1 Variant Curation Expert Panel: PVS1_Strong, PM2, PS4, PP1 (co-segregation with disease). c.2430delT (p.Phe810Leufs) - pathogenic (ClinGen EP) - The c.2430delT (p.Phe810Leufs*6) variant is predicted to result in a premature stop codon that leads to a truncated protein. However, it is located within the nonsense mediated decay resistance region upstream of c.2506G>T (p.Glu836*) (PVS1_Strong). This variant is absent in the gnomAD cohort (PM2; http://gnomad.broadinstitute.org). This variant has been reported in at least 4 families meeting HDGC clinical criteria (PS4; PMID 26182300, SCV000261293.4, SCV000218032.4). In summary, this variant meets criteria to be classified as pathogenic based on the ACMG/AMP criteria applied as specified by the CDH1 Variant Curation Expert Panel: PVS1_Strong, PM2, PS4. c.2506G>T (p.Glu836*) - Pathogenic (ClinGen EP) - CDH1 Variant Curation Expert Panel: PVS1_Strong, PM2, PS2 (de novo).
PS4_Supporting			Found in one family with diffuse gastric cancer - 2 of 3 variant carriers are affected (16 yo and 35 yo), while unaffected 34 yo (dad to 16 yo).
			Found in one family with diffuse gastric cancer - 2 affected, both under 40 yo. PubMed:9537325 

Not Met criteria codes

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
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	2 of 3 variant carriers affected with DGC - does not meet the criterion of 3-4 meioses.
			2 of 3 variant carriers affected with DGC - does not meet the criterion of 3-4 meioses. PubMed:9537325 
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
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
PM6		✖	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		✖	2 of 3 variant carriers affected with DGC - does not meet the criterion of 3-4 meioses. PubMed:9537325 
BS3		✖	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

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

Curation History 		
		
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