

Variant: NM_004360.4(CDH1):c.2398delC (p.Arg800Alafs)

CA281459 [↗](#)

156497 (ClinVar) [↗](#)

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

Condition: CDH1-related diffuse gastric and lobular breast cancer ([MONDO:0007648](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: a4959b72-3cf7-4e15-96c5-b96fd19dd327

Approved on: 2018-11-21

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HGVS expressions

NM_004360.4(CDH1):c.2398delC (p.Arg800Alafs)

NM_004360.4:c.2398delC

NC_000016.10:g.68829756del

CM000678.2:g.68829756del

NC_000016.9:g.68863659del

CM000678.1:g.68863659del

NC_000016.8:g.67421160del

NG_008021.1:g.97465del

ENST00000261769.10:c.2398del

ENST00000261769.9:c.2398del

ENST00000422392.6:c.2215del

ENST00000562118.1:n.616del

ENST00000562836.5:n.2469del

ENST00000566510.5:c.*1064del

ENST00000566612.5:c.*638del

ENST00000611625.4:c.2461del

ENST00000612417.4:c.1853+3202del

ENST00000621016.4:c.1866-4447del

NM_004360.3:c.2398del

NM_001317184.1:c.2215del

NM_001317185.1:c.850del

NM_001317186.1:c.433del

NM_004360.4:c.2398del

NM_004360.5:c.2398del

NM_001317184.2:c.2215del

NM_001317185.2:c.850del

NM_001317186.2:c.433del

NM_004360.5(CDH1):c.2398del (p.Arg800fs)

Pathogenic

Met criteria codes 4

PM2_Supporting

PVS1_Strong

PP1

PS4

Not Met criteria codes 22

BA1

BP2

BP3

BP1

BP4

BP5

BP7

BS2

BS3

BS4

BS1

PP2

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.2398delC (p.Arg800Alafs*16) 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). The variant is absent in the gnomAD cohort (PM2_Supporting; <http://gnomad.broadinstitute.org>). This variant has been reported in at least 4 families meeting HDGC clinical criteria (PS4; PMID 17545690). This variant was also found to co-segregation with disease in multiple affected family members, with 3 or 4 meioses observed (PP1; PMID: 17545690). 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 (Variant Interpretation Guidelines Version 3.1): PVS1_Strong, PM2_Supporting, PS4, PP1.

Met criteria codes

PM2_Supporting			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1_Strong			p.Arg800AlafsTer16. c.2398delC is located in the penultimate exon 15 of ENST00000261769.9 (NM_004360.4); penultimate exon 14 of ENST00000422392.6 (NM_001317184, NM_001317185, NM_001317186); and penultimate exon 16 of ENST00000611625.4. However this exon is not present in the alternatively spliced protein coding transcripts ENST00000621016.4 and ENST00000612417.4 which encode 647aa proteins. However, the premature stop codon (PTC) p.Arg800AlafsTer16 is in the final exon and not downregulated by NMD. Karam et al., 2008 PMID: 18427545 performed allele-specific expression analysis shows that the c.2398delC allele is not expressed at lower levels than the wild-type allele, suggesting c.2398delC transcripts are not downregulated by NMD The p.Arg800Alafs frameshift does alter a substantial portion of the Catenin binding domain (aa787-881) [possible PVS1_STRONG??], but is overall not a substatial proportion of the protein (<10% of 882aa) [PVS1_Moderate] Allele-specific expression analysis shows that the c.2398delC allele is not expressed at lower levels than the wild-type allele, suggesting c.2398delC transcripts are not downregulated by NMD PubMed:18427545 
PP1			3 families meet HDGC criteria (>2 gastric cancer cases; >1 diffuse gastric cancer). 1 additional family with 3 gastric cancer cases (not confirmed DGC), age of diagnosis 35-75 years. Cumulative risk by age 75 years in carriers for gastric cancer was 40% for males and 63% for females, and for breast cancer was 52% for females. All 4 families found to share common haplotype, suggesting a founder effect; and originate from the southeast coast of Newfoundland. 3 families meet HDGC criteria (>2 gastric cancer cases; >1 diffuse gastric cancer). 1 additional family with 3 gastric cancer cases (not confirmed DGC), age of diagnosis 35-75 years. Cumulative risk by age 75 years in carriers for gastric cancer was 40% for males and 63% for females, and for breast cancer was 52% for females. All 4 families found to share common haplotype, suggesting a founder effect; and originate from the southeast coast of Newfoundland. PubMed:17545690 
PS4			

Kaurah et al., PMID 17545690. 3 families meet HDGC criteria (>2 gastric cancer cases; >1 diffuse gastric cancer). 1 additional family with 3 gastric cancer cases (not confirmed DGC), age of diagnosis 35-75 years. Cumulative risk by age 75 years in carriers for gastric cancer was 40% for males and 63% for females, and for breast cancer was 52% for females. All 4 families found to share common haplotype, suggesting a founder effect; and originate from the southeast coast of Newfoundland. Plus internal lab data.

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Not Met criteria codes

BA1			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			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
BS2			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
BS4			3 families meet HDGC criteria (>2 gastric cancer cases; >1 diffuse gastric cancer). 1 additional family with 3 gastric cancer cases (not confirmed DGC), age of diagnosis 35-75 years. Cumulative risk by age 75 years in carriers for gastric cancer was 40% for males and 63% for females, and for breast cancer was 52% for females. All 4 families found to share common haplotype, suggesting a founder effect; and originate from the southeast coast of Newfoundland. PubMed:17545690

BS1			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			Kaurah et al., PMID 17545690. 3 families meet HDGC criteria (>2 gastric cancer cases; >1 diffuse gastric cancer). 1 additional family with 3 gastric cancer cases (not confirmed DGC), age of diagnosis 35-75 years. Cumulative risk by age 75 years in carriers for gastric cancer was 40% for males and 63% for females, and for breast cancer was 52% for females. All 4 families found to share common haplotype, suggesting a founder effect; and originate from the southeast coast of Newfoundland. Plus internal lab data. 3 families meet HDGC criteria (>2 gastric cancer cases; >1 diffuse gastric cancer). 1 additional family with 3 gastric cancer cases (not confirmed DGC), age of diagnosis 35-75 years. Cumulative risk by age 75 years in carriers for gastric cancer was 40% for males and 63% for females, and for breast cancer was 52% for females. All 4 families found to share common haplotype, suggesting a founder effect; and originate from the southeast coast of Newfoundland. PubMed:17545690 
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
PS1			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
PM3			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
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

Curation History



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