

Variant: NM_004360.4(CDH1):c.2396C>G (p.Pro799Arg)

CA163797 [↗](#)

140871 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: adcf805-c238-4e80-b9ad-f6fa541ab04d

Approved on: 2018-11-21

Published on: 2018-12-07

HGVS expressions

NM_004360.4:c.2396C>G

NM_004360.4(CDH1):c.2396C>G (p.Pro799Arg)

NC_000016.10:g.68829754C>G

CM000678.2:g.68829754C>G

NC_000016.9:g.68863657C>G

CM000678.1:g.68863657C>G

NC_000016.8:g.67421158C>G

NG_008021.1:g.97463C>G

ENST00000261769.10:c.2396C>G

ENST00000261769.9:c.2396C>G

ENST00000422392.6:c.2213C>G

ENST00000562118.1:n.614C>G

ENST00000562836.5:n.2467C>G

ENST00000566510.5:c.*1062C>G

ENST00000566612.5:c.*636C>G

ENST00000611625.4:c.2459C>G

ENST00000612417.4:c.1853+3200C>G

ENST00000621016.4:c.1866-4449C>G

NM_004360.3:c.2396C>G

NM_001317184.1:c.2213C>G

NM_001317185.1:c.848C>G

NM_001317186.1:c.431C>G

NM_004360.5:c.2396C>G

NM_001317184.2:c.2213C>G

NM_001317185.2:c.848C>G

NM_001317186.2:c.431C>G

NM_004360.5(CDH1):c.2396C>G (p.Pro799Arg)

Uncertain Significance

Met criteria codes **1**

PM2_Supporting

Not Met criteria codes **25**

PS2 PS4 PS3 PS1 BA1 PP4
PP1 PP2 PP3 PM3 PM1
PM4 PM5 PM6 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

BS1

BS2

BP5

BP7

BP2

BP3

BP1

BP4

PVS1

[↗](#) Criteria Specification Approval History

[↗](#) Criteria Specifications for this VCEP

Evidence Links

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Evidence submitted by expert panel

CDH1 VCEP

The c.2396C>G (p.Pro799Arg) variant is absent in the gnomAD cohort (PM2_Supporting; <http://gnomad.broadinstitute.org>). There is no other supporting data that meet criteria for consideration. In summary, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel (Variant Interpretation Guidelines Version 3.1): PM2_Supporting.

Met criteria codes

PM2_Supporting   absent in the gnomAD cohort

Not Met criteria codes

PS2   No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS4   No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS3   Conflicting functional studies

No increased cell motility due to Pro799Arg compared to WT or other missense variants tested. Also immunofluorescence microscopy indicate EGFR activation pattern for Pro799Arg was also similar to WT. [PubMed:19268661](#) 

P799R CDH1 has reduced staining at the plasma membrane and increased cytoplasmic accumulation. CDH1/PIPKly association is decreased for P799R, but not CDH1/p120 or CDH1/B-catenin association. Cell adhesion and invasion assays indicate P799R transfected cells form smaller aggregates but only slightly more invasive than WT [PubMed:22850631](#) 

Cell aggregation and Matrigel invasion assay using transfected cells suggests Pro799Arg has a pathogenic effect: Pro799Arg transfected cells fail to aggregate and are more invasive into Matrigel. [PubMed:15173255](#) 

PS1  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

PP4  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 

			SIFT, PolyPhen2-HVAR, LRT, MutationTaster, MutationAssessor, PROVEAN, and MetaLR predict deleterious. FATHMM, MetaSVM, and CADD predict tolerated. HSF predicts "Alteration of an exonic ESE site. Potential alteration of splicing." No change predicted by NNSPLICE.
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
PM6		✗	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		✗	Conflicting functional studies No increased cell motility due to Pro799Arg compared to WT or other missense variants tested. Also immunofluorescence microscopy indicate EGFR activation pattern for Pro799Arg was also similar to WT. PubMed:19268661  P799R CDH1 has reduced staining at the plasma membrane and increased cytoplasmic accumulation. CDH1/PIPKIγ association is decreased for P799R, but not CDH1/p120 or CDH1/B-catenin association. Cell adhesion and invasion assays indicate P799R transfected cells form smaller aggregates but only slightly more invasive than WT PubMed:22850631  Cell aggregation and Matrigel invasion assay using transfected cells suggests Pro799Arg has a pathogenic effect: Pro799Arg transfected cells fail to aggregate and are more invasive into Matrigel. PubMed:15173255 
BS1		✗	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

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			SIFT, PolyPhen2-HVAR, LRT, MutationTaster, MutationAssessor, PROVEAN, and MetaLR predict deleterious. FATHMM, MetaSVM, and CADD predict tolerated. HSF predicts "Alteration of an exonic ESE site. Potential alteration of splicing." No change predicted by NNSPLICE.
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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