The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_004360.4(CDH1):c.2195G>A (p.Arg732Gln)

CA16615410

406663 (ClinVar)

Gene: CDH1 (HGNC:999)
Condition: CDH1-related diffuse gastric and lobular breast cancer (MONDO:0007648)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0b968ecb-5432-4588-a812-7dd328f2b93d
Approved on: 2018-11-21
Published on: 2018-12-07

HGVS expressions

NM_004360.4:c.2195G>A
NM_004360.4(CDH1):c.2195G>A (p.Arg732Gln)
NC_000016.10:g.68828204G>A
CM000678.2:g.68828204G>A
NC_000016.9:g.68862107G>A
CM000678.1:g.68862107G>A
NC_000016.8:g.67419608G>A
NG_008021.1:g.95913G>A
ENST00000261769.10:c.2195G>A
ENST00000261769.9:c.2195G>A
ENST00000422392.6:c.2012G>A
ENST00000562118.1:n.413G>A
ENST00000562836.5:n.2266G>A
ENST00000566510.5:c.*861G>A
ENST00000566612.5:c.*435G>A
ENST00000611625.4:c.2258G>A
ENST00000612417.4:c.1853+1650G>A
ENST00000621016.4:c.1866-5999G>A
NM_004360.3:c.2195G>A
NM_001317184.1:c.2012G>A
NM_001317185.1:c.647G>A
NM_001317186.1:c.230G>A
NM_004360.5:c.2195G>A
NM_001317184.2:c.2012G>A
NM_001317185.2:c.647G>A
NM_001317186.2:c.230G>A
NM_004360.5(CDH1):c.2195G>A (p.Arg732Gln)

Pathogenic

Met criteria codes 3

PM2_Supporting PS4 PS3

Not Met criteria codes 23

BA1 PP4 PP1 PP2 PP3 PM6 PVS1 PM4 PM3 PM1 PM5 BS4 BS3 BS1 BS2

Expert Panel

CDH1 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen CDH1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 3.1*

PS2 PS1 BP5 BP7 BP3 BP2 BP1 BP4

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence Links 3

Evidence submitted by expert panel

CDH1 VCEP

The c.2195G>A variant is absent in the gnomAD cohort (PM2_Supporting; http://gnomad.broadinstitute.org). There is an RNA assay demonstrating an abnormal out-of-frame transcript for this variant (PS3; PMID: 17545690 15235021). This variant has also been reported in at least 12 families with HDGC criteria (PS4; PMID: 17545690 15235021 and laboratory internal data). 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): PM2_Supporting, PS3, PS4.

Met criteria codes

PM2_Supporting	✔	Absent from population databases
PS4	✔	At least 12 families are known to meet HDGC criteria. Variant identified in family meeting the following criteria: two or more documented cases of DGC in first degree relatives, with at least one diagnosed before age 50 PubMed:15235021 Variant identified in family with strong family history of GC, DGC, BC and LBC PubMed:17545690
PS3	✔	An RNA assay demonstrates the creation of abnormal out-of-frame transcript (RNA data: r.2165_2196del32p.I722KFS*15; laboratory internal data) Functional in vitro assays suggest that the variant affects cell-cell adhesion and cell invasion. PubMed:15235021 RT-PCR analysis demonstrated that the variant results in complex splicing and deletion of 32 base pairs at the start of exon 14. PubMed:17545690

Not Met criteria codes

BA1	✖	Absent from population databases
PP4	✖	Variant identified in family meeting the following criteria: two or more documented cases of DGC in first degree relatives, with at least one diagnosed before age 50 PubMed:15235021 Variant identified in family with strong family history of GC, DGC, BC and LBC PubMed:17545690
PP1	✖	Variant identified in proband's brother with GC dx at 65, but does not meet PP1_supporting (3-4 meioses)
PP2	✖	In silico analysis using the software NNSPLICE and NetGene2 predicted that the variant creates a new acceptor splice site. PubMed:17545690

PP3	✖	PS3 has been applied for the experimental data (RNA assay). In silico analysis using the software NNSPLICE and NetGene2 predicted that the variant creates a new acceptor splice site. PubMed:17545690
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	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
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
PM5	✖	A variant in the same codon and of uncertain significance (p.R732W) was identified in an individual with neuroblastoma. PubMed:26580448
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	In-frame splicing variant with in vitro functional studies
BS1	✖	Absent from population databases
BS2	✖	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
PS1	✖	A variant in the same codon and of uncertain significance (p.R732W) was identified in an individual with neuroblastoma. PubMed:26580448
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

BP3		✖	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
BP1		✖	In silico analysis using the software NNSPLICE and NetGene2 predicted that the variant creates a new acceptor splice site. PubMed:17545690
BP4		✖	Variant creates a new splice acceptor site. In silico analysis using the software NNSPLICE and NetGene2 predicted that the variant creates a new acceptor splice site. PubMed:17545690

Curation History

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