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

Version: 3.0

CA16615410

406663 (ClinVar)

Gene: CDH1 (HGNC:999)
Condition: CDH1-related diffuse gastric and lobular breast cancer (MONDO:0100488)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0b968ecb-5432-4588-a812-7dd328f2b93d
Approved on: 2023-11-27
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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

Pathogenic

Met criteria codes 3

PS3 PS4 PM2_Supporting

Not Met criteria codes 23

PS1 PS2 BP4 BP3 BP1 BP2 BP5 BP7 PVS1 BA1 PP1 PP2 PP3 PP4 PM1 PM3

Expert Panel

Criteria Specification Information

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

PM5 PM4 PM6 BS2 BS1 BS4 BS3

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

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
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
PM2_Supporting	✔	Absent from population databases

Not Met criteria codes

PS1	✖	A variant in the same codon and of uncertain significance (p.R732W) was identified in an individual with neuroblastoma. PubMed:26580448
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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

BP3		✖	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
BP2		✖	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
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	Absent from population databases
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
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
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		✖	A variant in the same codon and of uncertain significance (p.R732W) was identified in an individual with neuroblastoma. PubMed:26580448
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
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	Absent from population databases
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

Curation History

Showing 1 to 3 of 3 rows