Variant: NM_004004.6(GJB2):c.583A>G (p.Met195Val)

Version: 2.1

CA6904233

225375 (ClinVar)

Gene: GJB2
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 956244b5-ee05-47cd-98e0-a3c8fa5f5bc9
Approved on: 2024-05-15
Published on: 2024-07-08

HGVS expressions

NM_004004.6(GJB2):c.583A>G
NM_004004.6:c.583A>G
NM_004004.6(GJB2):c.583A>G (p.Met195Val)
NC_000013.11:g.20188999T>C
CM000675.2:g.20188999T>C
NC_000013.10:g.20763138T>C
CM000675.1:g.20763138T>C
NC_000013.9:g.19661138T>C
NG_008358.1:g.8977A>G
ENST00000382844.2:c.583A>G
ENST00000382848.5:c.583A>G
ENST00000382844.1:c.583A>G
ENST00000382848.4:c.583A>G
NM_004004.5:c.583A>G

Pathogenic

Met criteria codes 3

PP3 PS3_Moderate PM3_Very Strong

Not Met criteria codes 1

PM2

Evidence Links 1

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Hearing Loss Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CDH23, COCH, GJB2, KCNQ4, MYO6, MYO7A, SLC26A4, TECTA and USH2A Version 2*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.583A>G is a missense variant predicted to cause a substitution of methionine by valine at amino acid 195 (p.Met195Val). The highest population minor allele frequency in gnomAD v4.1.0 is 0.022% (16/44880, CI 95%) in the East Asian population (PM2_Supporting, BS1, and

BA1 are not met). This variant has been detected in 4 individuals with hearing loss with another pathogenic or suspected-pathogenic variant found in trans (4 PM3 points PMIDs: 24013081, 20497192, 30146550,33597575) (PM3_VeryStrong). It has also been identified in several probands with hearing loss in whom a second variant was not identified (PMIDs: 23555729, 19366456, 19125024, 27627659, 24507663). The computational predictor REVEL gives a score of 0.962 which is above the threshold of 0.7, evidence that correlates with impact to GJB2 function (PP3). Analysis in Hela cells demonstrated that the CX26-p.Met195Val protein was not transported to the cell membrane since there is an accumulation of the protein in the endoplasmic reticulum, indicating that this variant impacts protein function (PMID:26749107; PS3_Moderate). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive non-syndromic hearing loss based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP (PP3, PM3_VeryStrong, PS3_Moderate; Version 2; 5/15/24).

Met criteria codes

PP3	✔	REVEL: 0.962 Evolutionarily conserved No predicted splicing impact
PS3_Moderate	✔	Analysis in Hela cell line demonstrated that the CX26-p.Met195Val protein was not transported to the cell membrane. (accumulation of the protein in endoplasmic reticulum Analysis in Hela cell line demonstrated that the CX26-p.Met195Val protein was not transported to the cell membrane. (accumulation of the protein in endoplasmic reticulum **PubMed:26749107**
PM3_Very Strong	✔	4 cases counted (24013081, 30146550, 20497192,3359757)

Not Met criteria codes

PM2	✖	The highest minor allele frequency in gnomAD v.4: 0,022% (16/44880, CI 95%)) in East Asian alleles. Neither PM2_Supp nor BS1_Supp applied.

Curation History

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