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Variant: NM_004004.6(GJB2):c.584T>C (p.Met195Thr)

Version: 1.0

CA387460849

438620 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 288595d2-108b-486b-affa-9200bf31dcc8
Approved on: 2024/5/15
Published on: 2024/7/2

HGVS expressions

NM_004004.6(GJB2):c.584T>C (p.Met195Thr)
NM_004004.6:c.584T>C
NC_000013.11:g.20188998A>G
CM000675.2:g.20188998A>G
NC_000013.10:g.20763137A>G
CM000675.1:g.20763137A>G
NC_000013.9:g.19661137A>G
NG_008358.1:g.8978T>C
ENST00000382844.2:c.584T>C
ENST00000382848.5:c.584T>C
ENST00000382844.1:c.584T>C
ENST00000382848.4:c.584T>C
NM_004004.5:c.584T>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PM3 PM5 PS3_Moderate

Evidence Links 0

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.584T>C is a missense variant predicted to cause a substitution of methionine by threonine at amino acid 195 (p.Met195Thr). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0022% (4/60018, CI 95%) in the Admixed American population (PM2_Supporting). The c.584T>C variant has been detected in trans with c.35delG in one individual with moderate-severe hearing loss

(PMID: 19235794). The computational predictor REVEL gives a score of 0.968 which is above the threshold of 0.7, evidence that correlates with impact to GJB2 function (PP3). Another missense variant c.583G>C (p.Met195Val; ClinVar Variation ID: 22537) in the same codon has been classified as pathogenic for hearing loss by the ClinGen Hearing Loss VCEP (PM5). Analysis in Hela cells demonstrated that the CX26-p.Met195Thr protein formed a gap junction but with significantly decreased dye transfer. Additionally, electrophysiological characterization of the mutant in Xenopus oocytes resulted in a completely non-functional channel (PS3_Moderate; PMID: 23967136). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive non-syndromic hearing loss based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP (PM2_Supporting, PP3, PM3, PM5, PS3_Moderate; Version 2; 5/15/24).

Met criteria codes

PM2_Supporting	✔	The highest minor allele frequency in gnomAD v.4: 0,0022% (4/60018, CI 95%) in the Admixed American population.
PP3	✔	Revel score: 0.968
PM3	✔	This variant has been detected in trans with c.35delG variant in 1 individual with moderate-severe hearing loss (case data checked with the author of the paper: PMID: 19235794).
PM5	✔	Another missense variant c.583G>C p.Met195Val (ClinVar Variation ID: 22537) in the same codon has been classified as pathogenic for hearing loss by the ClinGen Hearing Loss VCEP
PS3_Moderate	✔	Analysis in Hela cell line demonstrated that the CX26-p.Met195Thr protein formed a gap junction but with significant decreased dye transfer. Besides, electrophysiological characterization of the mutant in Xenopus oocyte resulted in completely non-functional channel.

Curation History

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