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_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: 2024/5/15
Published on: 2024/7/8

HGVS expressions

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

Showing 1 to 3 of 3 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.