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Variant: NM_004004.6(GJB2):c.227T>C (p.Leu76Pro)

Version: 1.3

CA134953

44731 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4518ca08-03a8-48e9-a159-72760064fab8
Approved on: 2024/4/23
Published on: 2024/7/2

HGVS expressions

NM_004004.6(GJB2):c.227T>C (p.Leu76Pro)
NM_004004.6:c.227T>C
NC_000013.11:g.20189355A>G
CM000675.2:g.20189355A>G
NC_000013.10:g.20763494A>G
CM000675.1:g.20763494A>G
NC_000013.9:g.19661494A>G
NG_008358.1:g.8621T>C
ENST00000382844.2:c.227T>C
ENST00000382848.5:c.227T>C
ENST00000382844.1:c.227T>C
ENST00000382848.4:c.227T>C
NM_004004.5:c.227T>C

Likely Pathogenic

Met criteria codes 4

PP1 PP3 PM3_Strong PM2_Supporting

Evidence Links 0

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.227T>C is a missense variant in GJB2 predicted to cause substitution of leucine to proline at amino acid 76. The highest population minor allele frequency in gnomAD v4.1 is 0.0006779% (8/1180042) in the European (non-Finnish) population, which is a low enough frequency to apply PM2_Supporting based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2_Supporting). The variant has been detected in 4 probands with hearing loss (3.0 PM3 points). For two of those patients, a pathogenic variant was observed in trans (PMID: 17666888, 19274344), in a third the variant was observed in a homozygous state (ARUP Laboratories internal data, SCV001158697.1), and in the last patient the variant was observed with another pathogenic variant although with unknown phase (Partners LMM internal data, SCV000061486.5) (PM3_Strong). The variant has been reported to segregate with hearing loss in one affected family member (PP1, PMID: 19274344). The REVEL computational prediction tool produced a score of 0.976, which is above the threshold necessary to apply PP3. In summary, this variant meets criteria to be classified as likely pathogenic for

autosomal recessive nonsyndromic hearing loss based on the ACMG/AMP criteria applied as specified by the ClinGen Hearing Loss Expert Panel : PM3_Strong, PM2_Supporting, PP1, PP3. (The ClinGen Hearing Loss VCEP Specifications Version 2, 04/17/2024)

Met criteria codes

PP1	✔	Two siblings in a Brazilian family with NSHL with this variant and the c.35delG variant present in trans.
PP3	✔	The REVEL score is 0.976 and conserved across all vertebrates in UCSC genome browser except the cavefish and Southern Platyfish. No splicing impact predicted by MaxEntScan.
PM3_Strong	✔	Total of 3 PM3 point. 0.5 points for a homozygous presence of the variant in one individual with pre-lingual SNHL and 0.5 points for another proband with another pathogenic GJB2 variant with unknown phase. 1 point was scored for the Putcha proband and 1 point was scored for the Batissoco proband.
PM2_Supporting	✔	Variant is present in 0.0006779% (8/1180042) of European (non-Finnish) chromosomes in gnomAD v4.1.0 (PM2_Supporting).

Curation History

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