

Variant: *NM_004004.5(GJB2):c.516G>C (p.Trp172Cys)*

Version: 1.0

CA387460990 [↗](#)

590799 (ClinVar) [↗](#)

Gene: GJB2 ([HGNC:2706](#))

Condition: nonsyndromic genetic deafness ([MONDO:0019497](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 73289133-df78-471e-83a2-9429ae616f4e

Approved on: 2019/7/28

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HGVS expressions

NM_004004.5:c.516G>C

NM_004004.5(GJB2):c.516G>C (p.Trp172Cys)

NC_000013.11:g.20189066C>G

CM000675.2:g.20189066C>G

NC_000013.10:g.20763205C>G

CM000675.1:g.20763205C>G

NC_000013.9:g.19661205C>G

NG_008358.1:g.8910G>C

ENST00000382844.2:c.516G>C

ENST00000382848.5:c.516G>C

ENST00000382844.1:c.516G>C

ENST00000382848.4:c.516G>C

NM_004004.6:c.516G>C

Pathogenic

Met criteria codes 4

PP1_Strong

PS4

PP3

PM3_Supporting

Not Met criteria codes 2

BA1

PM2

Evidence Links 3

Expert Panel

Hearing Loss VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hearing Loss VCEP

The p.Trp172Cys variant in the GJB2 gene was absent from gnomAD (PM2). However, this variant has been identified at an allele frequency of 1.9% (6/314) in unaffected Tuvian individuals (PMID: 20201936). This frequency would normally lead to application of BA1 based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss variants (BA1). However, the variant was found to have a statistically higher prevalence in affected Tuvian individuals (66/440 alleles) over ethnically-matched controls (6/314 alleles) (15% vs 1.9%; $p < 0.0001$, PS4; PMID: 20201936) suggesting that this is actually a high frequency founder variant in this population. This variant has been detected in trans with two pathogenic variants in probands with hearing loss (PM3_supporting PMID:20201936; 15790391). The p.Trp172Cys variant in GJB2 has been reported to segregate with hearing loss in at least 9 affected family members

(PP1_Strong; PMID: 20201936). The REVEL computational prediction analysis tool produced a score of 0.7 (rounded up from 0.687), which is above the threshold necessary to apply PP3. In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive hearing loss based on the ACMG/AMP criteria applied as specified by the Hearing Loss Expert Panel (PS4, PP1_Strong, PP3, PM3_supporting).

Met criteria codes

PP1_Strong			The variant segregated with hearing loss in 9 affected individuals. There were also 14 unaffected individuals with a LOD of >6.67 PMID: 20201936
PS4			<p>A 2x2 conttingency analysis of total variant alleles in cases v controls was performed. The variant is present in 66/440 case alleles and 6/314 control alleles. With a fisher exact test, the p value is <0.0001. which is highly significant.</p> <p>220 Tuvinians (Southern Siberia, Russia) with hearing loss were tested for variants in GJB2. The p.Trp172Cys accounted for 62.9% of all mutant GJB2 alleles. It was present in 25 homozygous individuals, 7 compound heterozygous individuals (with c.-23+1G>A, and in 9 heterozygotes. This variant was not found to be biallelic in any of the 157 ethnically-matched controls, but it was observed in 6 carriers. PubMed:31195736 </p>
PP3			The REVEL score for this variant is 0.687 and the pathogenic cutoff for the hearing loss group is >/= 0.7. The variant is well-conserved and no species harbor the variant amino acid. Splicing predictors predict no change. The group has decided on 7/16/19 to round this score up to 0.7 and mark PP3 as met.
PM3_Supporting			<p>With the new specifications (and this variant meeting BA1), these two cases would only count as 0.1 points each, 0.2 points total. PM3 is not met. However, after group discussion, we felt that the Tuvinian population is too small to use the new PM3 rule, but decided to downgrade it to PM3_supporting because of the frequency in Tuvinian controls.</p> <p>76 Altaian (South Siberia, Russia) individuals with NSHL were tested for variants in GJB2, GJB6 deletions, and mitochondrial variants. The p.Trp172Cys variant was identified in one individual who was compound het for the c.235delC variant. It was absent from 130 unrelated Altaian controls. PubMed:15790391 </p> <p>534 Mongolian individuals with hearing loss were tested for variants in GJB2. The p.Trp172Cys variant was identified in one individual who was compound het for the c.299_300delAT. It was absent from 217 controls. PubMed:20201936 </p>

Not Met criteria codes

BA1			The p.Trp172Cys variant in GJB2 is absent from gnomAD with adequate coverage. However, it is present in 6/314 Tuvinian control alleles (1.9%) (PMID: 31195736). The expert group decided that BA1 would not be met because the Tuvinian population is a very small sub-population.
PM2			The p.Trp172Cys variant in GJB2 is absent from gnomAD with adequate coverage. However, it is present in 6/314 Tuvinian control alleles (1.9%) (PMID: 31195736)

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Showing 1 to 1 of 1 rows

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