

Variant: *NM_004004.6(GJB2):c.56G>C (p.Ser19Thr)*

Version: 2.1

CA342005 [↗](#)

21389 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: bd25523c-7613-4d08-9a6e-9cbcc2a5eb4b

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HGVS expressions

NM_004004.6:c.56G>C

NM_004004.6(GJB2):c.56G>C (p.Ser19Thr)

NC_000013.11:g.20189526C>G

CM000675.2:g.20189526C>G

NC_000013.10:g.20763665C>G

CM000675.1:g.20763665C>G

NC_000013.9:g.19661665C>G

NG_008358.1:g.8450G>C

ENST00000382844.2:c.56G>C

ENST00000382848.5:c.56G>C

ENST00000382844.1:c.56G>C

ENST00000382848.4:c.56G>C

NM_004004.5:c.56G>C

Pathogenic

Met criteria codes **4**

PS3_Moderate

PM3_Very Strong

PP1

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 variant NM_004004.6:c.56G>C in GJB2 is a missense variant predicted to cause substitution of serine by threonine at amino acid 19 (p.Ser19Thr). The highest filtering allele frequency in gnomAD v4 is 0.00111% (19/1111946 CI 95%) in the non-Finnish European population (PM2_Supporting). This variant has been detected in 5 probands with hearing loss. For 4 of those probands, a pathogenic or suspected-pathogenic variants was observed in trans (PM3_VeryStrong; PMIDs: 16077952, 26553399, 10982180, 15146474, Partners Laboratory for Molecular Medicine internal data). Of note, 1 proband was compound-heterozygous for Ser19Thr with c.35delG and also carried Arg32Ser in cis; another proband had Ser19Thr, Arg32Ser and E47* in unspecified zygosity though it is assumed that Ser19Thr and Arg32Ser were in cis based on prior observation. These cases were not counted towards PM3 because contribution of the Arg32Ser variant can not be ruled out. The p.Ser19Thr variant has been reported to segregate with hearing loss in one affected family member (PP1, PMID: 16077952). A functional study has shown that p.Ser19Thr impacts protein function (PS3_Moderate; PMID: 12176036). In summary, this variant meets the

criteria to be classified as pathogenic for autosomal recessive nonsyndromic sensorineural hearing loss, based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM3_VeryStrong, PS3_Moderate, PM2_Supporting, PP1 (ClinGen Hearing Loss VCEP specifications version 2; 1/3/24).

Met criteria codes

PS3_Moderate			Dye transfer study with non-transfected HeLa cells used as a negative control did not display intercellular dye transfer. No dye was observed between clusters of cells expressing the S19T variant (PMID: 12176036).
PM3_Very Strong			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			Italian family with 2 affecteds compound-het with M34T and S19T (PMID: 16077952)
PM2_Supporting			The filtering allele frequency is 0.00111% (19/1111946 CI 95%) non-Finnish European chromosomes in gnomAD v4.

Curation History

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