

Variant: *NM_004004.6(GJB2):c.339T>G (p.Ser113Arg)*

Version: 1.2

CA342004 [↗](#)

21385 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 88473ffb-e617-4c19-af9c-0ca3bb39ff23

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HGVS expressions

NM_004004.6:c.339T>G

NM_004004.6(GJB2):c.339T>G (p.Ser113Arg)

NC_000013.11:g.20189243A>C

CM000675.2:g.20189243A>C

NC_000013.10:g.20763382A>C

CM000675.1:g.20763382A>C

NC_000013.9:g.19661382A>C

NG_008358.1:g.8733T>G

ENST00000382844.2:c.339T>G

ENST00000382848.5:c.339T>G

ENST00000382844.1:c.339T>G

ENST00000382848.4:c.339T>G

NM_004004.5:c.339T>G

Uncertain Significance

Met criteria codes **2**

PS3_Moderate

PM3

Not Met criteria codes **5**

BA1

BS1

BP4

PP3

PM2

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.339T>G variant in GJB2 is a missense variant predicted to cause substitution of serine by arginine at amino acid 113. The highest population minor allele frequency in gnomAD v4.0.0 is 0.02% (7/26136 alleles) in the Ashkenazi Jewish population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL provides a score of 0.553 which is neither above nor below the thresholds

predicting a damaging or benign impact on GJB2 function (PP3 and BP4 are not met). An in vitro functional study performed in Xenopus oocytes showed that variant junctional conductance for p.Ser113Arg was similar to water (negative control), indicating a loss of function impact on protein function (PS3_Moderate; PMID:12505163). The p.Ser113Arg variant has been reported in several probands with hearing loss, including 3 individuals with a second pathogenic variant without phase confirmation (1.5 points, PM3, PMID: 15365987, 11439000, 9529365, 16380907, 24078562). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for nonsyndromic genetic hearing loss based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PS3_Moderate, PM3. (ClinGen Hearing Loss VCEP specifications version 2; 01/17/2024).

Met criteria codes

PS3_Moderate			An in vitro functional study performed in Xenopus oocytes showed that variant junctional conductance for p.Ser113Arg was similar to water (negative control), indicating a loss of function impact on protein function (PS3_Moderate; PMID:12505163).
PM3			The p.Ser113Arg variant has been reported in several probands with hearing loss, and 3 individuals with a second pathogenic variant without phase confirmation (PM3, PMID: 15365987, 11439000, 9529365, 16380907, 24078562).

Not Met criteria codes

BA1			The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002981 (3/10064 alleles) in the Ashkenazi Jewish population (PM2_Supporting, BS1, and BA1 are not met).
BS1			The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002981 (3/10064 alleles) in the Ashkenazi Jewish population (PM2_Supporting, BS1, and BA1 are not met).
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL: 0.553 (no criteria met)
PM2			The highest population minor allele frequency in gnomAD v4.0.0 is 0.0002678 (7/26136 alleles) in the Ashkenazi Jewish population (PM2_Supporting, BS1, and BA1 are not met).

Curation History 

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