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.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
Approved on: 2024/1/17
Published on: 2024/4/1

HGVS expressions

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

BS1 BP4 BA1 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

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
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).
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

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.