

Variant: *NM_004004.6(GJB2):c.34G>T (p.Gly12Cys)*

CA172224 [↗](#)

44740 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 060eab50-f9a8-40d2-b449-2edd2f54e4f3

Approved on: 2018-09-11

Published on: 2018-12-10

HGVS expressions

NM_004004.6:c.34G>T

NM_004004.6(GJB2):c.34G>T (p.Gly12Cys)

NC_000013.11:g.20189548C>A

CM000675.2:g.20189548C>A

NC_000013.10:g.20763687C>A

CM000675.1:g.20763687C>A

NC_000013.9:g.19661687C>A

NG_008358.1:g.8428G>T

ENST00000382844.2:c.34G>T

ENST00000382848.5:c.34G>T

ENST00000382844.1:c.34G>T

ENST00000382848.4:c.34G>T

NM_004004.5:c.34G>T

Likely Pathogenic

The Expert Panel has overridden the computationally generated classification - "Uncertain Significance - Conflicting Evidence"

Met criteria codes 4

PP3 BS1 PM5 PM3_Very Strong

Not Met criteria codes 22

PS3 PS4 PS2 PS1 PP1 PP4
PP2 BA1 BS2 BS3 BS4
PM6 PM2 PM1 PM4 BP5
BP7 BP2 BP3 BP1 BP4
PVS1

Evidence Links 5

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

[↗](#) **Criteria Specification Approval History**

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

Evidence submitted by expert panel

Hearing Loss VCEP

The c.34G>T (NM_004004.6) in GJB2 is a missense variant predicted to cause the substitution of glycine by cysteine at amino acid 12 (p.Gly12Cys). The highest population minor allele frequency in gnomAD v2.1.1 is 0.0036 (128/35104 alleles) in the Latino/Admixed American population, which is higher than the ClinGen Hearing Loss VCEP threshold (>0.003) for BS1, and therefore meets this criterion (BS1). This is a high enough frequency that, in absence of conflicting data, might warrant a likely benign classification based on the

thresholds defined by the ClinGen Hearing Loss VCEP for autosomal recessive hearing loss variants. However, based on the evidence outlined below, the ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for nonsyndromic hearing loss outweighs its high allele frequency in population databases. Therefore, the BS1 code will not contribute to the overall classification. This variant has been detected in at least 10 patients with hearing loss. Of those individuals, at least 4 were compound heterozygous or the variant and a pathogenic or likely pathogenic variant was observed in trans and one proband was homozygous for the variant (c.35delG, p.V37I, p.Val198fs, p.Lys122Ile, PMID: 15365987, 17041943, 17666888, 25288386, 26969326, 31035178, SCV000061501.5) (PM3_Very Strong). A different pathogenic missense variant (p.Gly12Val) (ClinVar Variation ID 21387) in the same codon of GJB2 has been classified as likely pathogenic and pathogenic for hearing loss by 7 labs who are in concordance that this variant is LP/P (PM5). The computational predictor REVEL gives a score of 0.838, and the nucleotide is heavily conserved in UCSC, which is above the threshold of 0.7, evidence that correlates with impact to GJB2 function (PP3). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive nonsyndromic genetic hearing loss based on the ACMG/AMP criteria applied as specified by the Hearing Loss VCEP: PM3_Very Strong, PM5, PP3, BS1 (ClinGen Hearing Loss VCEP specifications version 2; 10/19/2022)

Met criteria codes

PP3			REVEL score is 0.838, and the nucleotide is heavily conserved in UCSC
BS1			While this variant technically meets the BS1 cutoff 0.36%(128/35104) Latino/Admixed American population, it is on the ClinGen Hearing Loss Expert Panel exclusion list.
PM5			p.Gly12Arg (ClinVar ID: 21387) has been submitted by literature only as a pathogenic variant in ClinVar by a 0 star submission. The p.Gly12Val variant in GJB2 has been submitted by 10+ labs who are in concordance that this variant is LP/P. While the p.Gly12Arg variant may need more evidence to be considered a path variant by our standards, the p.Gly12Val variant has sufficient evidence to apply PM5 for this variant.
PM3_Very Strong			This variant has been detected in at least 10 patients with hearing loss. Of those individuals, at least 4 were compound heterozygous or the variant and a pathogenic or likely pathogenic variant was observed in trans and one was homozygous for the variant (c.35delG, p.V37I, p.Val198fs, p.Lys122Ile, PMID: 15365987, 17041943, 17666888, 25288386, 26969326, 31035178, SCV000061501.5) (PM3_Very Strong)

Not Met criteria codes

PS3			There is no functional evidence for this variant. There is a fair amount of functional evidence for the p.Gly12Arg variant in GJB2 at this codon, but that cannot be counted here.
PS4			attempted to use case-control as there are 10 reported alleles in HL cases in the literature out of 21004 total alleles screened There are 130/271738 alleles in gnomAD with the variant (used the total because all reports were multiethnic) but the graphpad software only allows a denominator of 123456, therefore, 10/21004 was compared to the frequency in the general population equal to that of 130/271738 but with a denominator of 123456. Which equals 59/123456. The frequency differential between cases and the general population was NOT significant.

78 individuals in cohort w/ congenital HL form Northeastern Mexico. Identified presumably 1 het individual. Other allele not identified. Largely non European but they also have a multiethnic cohort. [PubMed:25288386](#)

Testing of 1294 persons with deafness at Molecular Otolaryngology Research Laboratories identified 1 person carrying only this GJB2 variant in a heterozygous state. There were 88 other individuals who oly had one identified variant. Assumed multiethnic cohort. [PubMed:15365987](#)

Identified the variant in 3 heterozygous cases in a screening of 610 deaf probands. Variant was not found in 294 controls. Clinical info for one proband: Hispanic w/ family history consistent with autosomal dominant hearing loss.

Assumed multiethnic cohort as controls have about 150 AA, Hisp., Asian, and Caucasians each.

[PubMed:17041943](#)

7401 deaf probands screened. The variant was identified in a heterozygous state in 4 of the individuals. Multiethnic cohort.

[PubMed:17666888](#)

One patient with congenital SNHL, reported inheritance was AD, as the variant was in trans with a p.Tyr68Cys variant that is thought to be LB. Cohort is multiethnic

[PubMed:26969326](#)

PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			GJB2 does not have a specified phenotype associated with it.
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			There is no functional evidence for this variant. There is a fair amount of functional evidence for the p.Gly12Arg variant in GJB2 at this codon, but that cannot be counted here.
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			REVEL prediction higher than 0.7
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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