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.110T>C (p.Val37Ala)

Version: 2.0

CA6904317

449490 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1d8c5ad9-8453-4ae4-8c22-1b4c7b044189
Approved on: Wed, 19 Aug 2026 00:00:00 +0000
Published on: Wed, 30 Sep 2026 00:00:00 +0000

HGVS expressions

NM_004004.6:c.110T>C
NM_004004.6(GJB2):c.110T>C (p.Val37Ala)
NM_004004.6(GJB2):c.110T>C
NC_000013.11:g.20189472A>G
CM000675.2:g.20189472A>G
NC_000013.10:g.20763611A>G
CM000675.1:g.20763611A>G
NC_000013.9:g.19661611A>G
NG_008358.1:g.8504T>C
ENST00000382844.2:c.110T>C
ENST00000382848.5:c.110T>C
ENST00000382844.1:c.110T>C
ENST00000382848.4:c.110T>C
NM_004004.5:c.110T>C

Pathogenic

Met criteria codes 2

PM5_Strong PM3_Strong

Not Met criteria codes 3

PM2 PS3 PP3

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 2.0*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.110T>C variant in GJB2 is a missense variant predicted to cause substitution of valine by alanine at amino acid 37 (p.Val37Ala). The highest population minor allele frequency in gnomAD v4.1.1 is 0.0337% (25/74924 alleles-African/African American, PM2_Supporting, BA1,

and BS1 not met). The computational predictor REVEL yields a score of 0.675 (PP3 not met). This variant has been identified in 11 patients who did not harbor a second variant in GJB2 (PMID 21287563, 17666888, 15365987, GeneDx internal data, Invitae internal data), but has also been detected in two patients in trans with pathogenic/likely pathogenic variants c.167delT (p.Leu56Argfs*26), c.132G>A (p.Trp44Ter) and one predicted in trans with pathogenic/likely pathogenic c.647_650delGATA (p.Arg216Ilefs*17) (2.5 points, PM3_Strong met; Partners Laboratory for Molecular Medicine SCV000967620.2, Molecular Otolaryngology and Renal Research Laboratories internal data). Two different missense variants at this codon (p.Val37Ile ClinVar ID:17023; and p.Val37Phe ClinVar ID:179256) have been classified as pathogenic or likely pathogenic for autosomal recessive non-syndromic HL by the ClinGen HL-VCEP (PM5_Strong met). In summary, based on the current evidence, the variant NM_004004.6(GJB2):c.110T>C (p.Val37Ala) meets the criteria to be classified as pathogenic for autosomal recessive non-syndromic HL based on the ACMG/AMP criteria applied as specified by the ClinGen HL-VCEP: PM3_Strong, PM5_Strong (ClinGen Hearing Loss VCEP specifications version 2; 8/19/2026).

Met criteria codes

PM5_Strong	✔	Two different pathogenic missense variants (p.Val37Ile and p.Val37Phe) have been previously identified at this codon of GJB2 which may indicate that this residue is critical to the function of the protein (PM5_Strong, p.Val37Ile ClinVar Variation ID 17023, PMID 31160754; p.Val37Phe ClinVar Variation ID:179256 PMID: 37108562)).
PM3_Strong	✔	This variant has been identified in 11 patients who did not harbor a second variant in GJB2 (PMID 21287563, 17666888, 15365987, GeneDx internal data, Invitae internal data), but has also been detected in two patients in trans with pathogenic/likely pathogenic variants c.167delT (p.Leu56Argfs*26), c.132G>A (p.Trp44Ter) and one predicted in trans with pathogenic/likely pathogenic c.647_650delGATA (p.Arg216Ilefs*17) (2.5 points, PM3_Strong met; Partners Laboratory for Molecular Medicine SCV000967620.2, Molecular Otolaryngology and Renal Research Laboratories internal data).

Not Met criteria codes

PM2	✖	The highest population minor allele frequency in gnomAD v4.1.1 is 0.0337% (25/74924 alleles-African/African American, PM2_Supporting, BA1, and BS1 not met).
PS3	✖	Bioinformatic analysis was used to predict the effect of the p.Val37Ala variant on GJB2 and molecular modeling determined that there may be a loss of protein structure. However, because no in vitro or in vivo experiments were done, this was not counted towards PS3.
PP3	✖	The computational predictor REVEL yields a score of 0.675 (PP3 not met).

Curation History

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