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: 1.1

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: 2024-04-22
Published on: 2024-07-02

HGVS expressions

NM_004004.6(GJB2):c.110T>C
NM_004004.6:c.110T>C
NM_004004.6(GJB2):c.110T>C (p.Val37Ala)
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

Likely Pathogenic

Met criteria codes 3

PP3 PM3 PM5_Strong

Not Met criteria codes 2

PS3 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.1101T>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 filtering allele frequency in gnomAD v4 is 0.03% (25/74924 alleles) in the African American population

(PM2_Supporting, BA1, and BS1 not met). This variant has been identified in 11 heterozygous individuals who did not harbor a second variant in GJB2 (PMID 21287563, PMID 17666888, PMID 15365987,GeneDx Internal Data, Invitae Internal Data), but has also been detected in 1 patient with hearing loss in trans with a pathogenic variant (1 point, PM3; Partners LMM internal data SCV000967620.2, GeneDx Internal Data, Invitae Internal Data). The REVEL computational prediction analysis tool produced a score of 0.675, which rounded up to 0.7 is above the threshold necessary to apply PP3 (PP3). 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). In summary, this variant meets criteria to be classified as likely pathogenic for autosomal recessive nonsyndromic hearing loss based on the ACMG/AMP criteria applied as specified by the ClinGen Hearing Loss VCEP: PM3, PM5_Strong, PP3. (Hearing Loss VCEP specifications version 2; 4/22/2024)

Met criteria codes

PP3	✔	The REVEL score is 0.675, which is lower than our pathogenic cutoff of 0.7. However, the HL VCEP experts have voted to round up and apply PP3.
PM3	✔	This variant has been identified in 11 heterozygous individuals who did not harbor a second variant in GJB2 (PMID 21287563, PMID 17666888, PMID 15365987,GeneDx Internal Data, Invitae Internal Data), but has also been detected in 1 patient with hearing loss in trans with a pathogenic variant (1 point, PM3; Partners LMM internal data SCV000967620.2, GeneDx Internal Data, Invitae Internal Data).
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)).

Not Met criteria codes

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.
PM2	✖	The highest population filtering allele frequency in gnomAD v4 is 0.03% (25/74924 alleles) in the African American population (PM2_Supporting, BA1, and BS1 not met).

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_004004.6(GJB2):c.110T>C (p.Val37...	Likely Pathogenic	Nonsyndromic Genetic Deafness	2024-07-02	1.1	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	GJB2
View	NM_004004.6(GJB2):c.110T>C (p.Val37...	Likely Pathogenic	Nonsyndromic Genetic Deafness	2020-07-28	1.0	-	GJB2

Showing 1 to 2 of 2 rows