

Variant: *NM_004004.6(GJB2):c.677T>G (p.Val226Gly)*

Version: 1.1

[CA6904209](#)

[447450 \(ClinVar\)](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UID: 2b5171d0-5733-4e05-a77e-5d32d43be312

Approved on: 2023-09-26

Published on: 2023-10-05

HGVS expressions

NM_004004.6:c.677T>G

NM_004004.6(GJB2):c.677T>G (p.Val226Gly)

NC_000013.11:g.20188905A>C

CM000675.2:g.20188905A>C

NC_000013.10:g.20763044A>C

CM000675.1:g.20763044A>C

NC_000013.9:g.19661044A>C

NG_008358.1:g.9071T>G

ENST00000382844.2:c.677T>G

ENST00000382848.5:c.677T>G

ENST00000382844.1:c.677T>G

ENST00000382848.4:c.677T>G

NM_004004.5:c.677T>G

Uncertain Significance

Met criteria codes **1**

PM2

Not Met criteria codes **25**

BP5 BP7 BP4 BP3 BP1 BP2

PVS1 PS1 PS2 PS3 PS4

PP1 PP2 PP3 PP4 PM6

PM1 PM3 PM5 PM4 BA1

BS1 BS4 BS3 BS2

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.677T>G variant in GJB2 is a missense variant predicted to cause substitution of valine to glycine at amino acid 226. The highest population minor allele frequency in gnomAD v2.1.1 is 0.003% (1/35370) in Latino/Admixed American chromosomes, which is below the PM2_Supporting thresholds defined by the ClinGen Hearing Loss Expert Panel ($\leq 0.007\%$) for autosomal recessive disorders





























(PM2_Supporting). The computational predictor REVEL gives a score of 0.586 which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function (no criteria met). It has been reported in the literature in one heterozygous individual with hearing loss; however, a second variant was not identified and there was no reported family history of hearing loss (no criteria met; PMID: 17666888). This variant has been reported by several clinical laboratories in ClinVar as a variant of uncertain significance (ClinVar Variation ID: 447450). Internal laboratory evidence indicates that the variant has been identified in at least three individuals with hearing loss in the heterozygous state without a second GJB2 variant. One individual was reported to have multiple affected relatives; however, segregation data was not available (no criteria met; SCV000613524.1, SCV000731317.1, SCV002817016.1, SCV002179797.2). In summary, this variant is classified as a variant of uncertain significance based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP; PM2_Supporting. The ClinGen Hearing Loss VCEP Specifications Version 2; 09/26/2023.

Met criteria codes

PM2		This allele is present in 0.003% of Latino alleles which is below the PM2 cutoff of 0.007% for recessive hearing loss.
------------	---	--

Not Met criteria codes

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
BP4			The REVEL score of 0.586 falls in between what is predicted to be pathogenic/benign.
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
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			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
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS4			There are 2 het cases (one with breast or ovarian cancer and one with HL). No mention of HL status in cancer patient.
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			The REVEL score of 0.586 falls in between what is predicted to be pathogenic/benign.
PP4			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
PM1			HLWG only uses this rule for the pore domain of KCNQ4
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			The p.Val226Asp variant is a VUS in ClinVar.
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			This allele is present in 0.003% of Latino alleles which is below the PM2 cutoff of 0.007% for recessive hearing loss.
BS1			This allele is present in 0.003% of Latino alleles which is below the PM2 cutoff of 0.007% for recessive hearing loss.
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			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

	▼	▼
--	---	---

Showing 1 to 2 of 2 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.