Variant: NM_004004.6(GJB2):c.23C>T (p.Thr8Met)

Version: 1.1

CA6904332

379889 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8756501e-0855-4fe3-9e70-64b3569c122e
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HGVS expressions

NM_004004.6:c.23C>T
NM_004004.6(GJB2):c.23C>T (p.Thr8Met)
NC_000013.11:g.20189559G>A
CM000675.2:g.20189559G>A
NC_000013.10:g.20763698G>A
CM000675.1:g.20763698G>A
NC_000013.9:g.19661698G>A
NG_008358.1:g.8417C>T
ENST00000382844.2:c.23C>T
ENST00000382848.5:c.23C>T
ENST00000382844.1:c.23C>T
ENST00000382848.4:c.23C>T
NM_004004.5:c.23C>T

Uncertain Significance

Met criteria codes 2

PS3_Supporting PM3

Not Met criteria codes 6

BS1 PP2 PP3 PM2 BA1 BP4

Evidence Links 1

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.23C>T variant in GJB2 is a missense variant predicted to cause substitution of threonine by methionine at amino acid 8. The filtering allele frequency (the lower threshold of the 95% CI of 75/91084, 1 homozygote) of this variant is 0.06728% in the South Asian chromosomes by gnomAD v4.1.0, which is neither above nor below the thresholds defined by the ClinGen HL EP for autosomal recessive

conditions (PM2_Supporting, BS1, and BA1 not met). The computational predictor REVEL gives a score of 0.632, which is neither above nor below the thresholds predicting a damaging or benign impact on GJB2 function. Dual whole cell voltage clamp and dye transfer assays in HeLa cells demonstrated that even though potassium permeability remains the same in the variant, there is a reduction in cationic and large molecules dye transfer compared to WT (PMID:18684989) (PS3_Supporting). This variant has been detected in at least two individuals with autosomal recessive NSHL. One was compound heterozygous for the variant and a pathogenic variant, c.109G>A (p.Val37Ile), with phase unknown (0.5 PM3 points, PMID: 22384008). One individual was homozygous for the variant (0.5 PM3 points, PMID: 31162818) (PM3). In summary, this variant meets the criteria to be classified as uncertain significance for autosomal recessive nonsyndromic genetic hearing loss based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM3, PS3_Supporting (Hearing Loss VCEP specifications version 2; 01/15/2025).

Met criteria codes

PS3_Supporting	✔	Dual whole cell voltage clamp and dye transfer assays in HeLa cells demonstrated that even though potassium permeability remains the same in the variant, there is a reduction in cationic and large molecules dye transfer compared to WT (PMID:18684989) (PS3_Supporting). Dual whole cell voltage clamp and dye transfer assays in HeLa cells demonstrated that even though potassium permeability remains the same in the variant, there is a reduction in cationic and large molecules dye transfer compared to WT (PMID:18684989) (PS3_Supporting). **PubMed:18684989**
PM3	✔	This variant has been detected in at least two individuals with autosomal recessive NSHL. One was compound heterozygous for the variant and a pathogenic variant, c.109G>A (p.Val37Ile), with phase unknown (0.5 PM3 points, PMID: 22384008). One individual was homozygous for the variant (0.5 PM3 points, PMID: 31162818) (PM3).

Not Met criteria codes

BS1	✖	The filtering allele frequency (the lower threshold of the 95% CI of 75/91084, 1 homozygote) of this variant is 0.06728% in the South Asian chromosomes by gnomAD v4.1.0, which is neither above nor below the thresholds defined by the ClinGen HL EP for autosomal recessive conditions (PM2_Supporting, BS1, and BA1 not met).
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	The computational predictor REVEL gives a score of 0.632, which is neither above nor below the thresholds predicting a damaging or benign impact on GJB2 function.
PM2	✖	The filtering allele frequency (the lower threshold of the 95% CI of 75/91084, 1 homozygote) of this variant is 0.06728% in the South Asian chromosomes by gnomAD v4.1.0, which is neither above nor below the thresholds defined by the ClinGen HL EP for autosomal recessive conditions (PM2_Supporting, BS1, and BA1 not met).
BA1	✖	The filtering allele frequency (the lower threshold of the 95% CI of 75/91084, 1 homozygote) of this variant is 0.06728% in the South Asian chromosomes by gnomAD v4.1.0, which is neither above nor below the thresholds defined by the ClinGen HL EP for autosomal recessive conditions (PM2_Supporting, BS1, and BA1 not met).
BP4	✖	The computational predictor REVEL gives a score of 0.632, which is neither above nor below the thresholds predicting a damaging or benign impact on GJB2 function.

Curation History

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