Variant: NM_206933.4(USH2A):c.12505A>G (p.Thr4169Ala)

Version: 2.1

CA179513

166435 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 67f5ff79-03db-45e0-a679-81f69e505882
Approved on: 2025-05-21
Published on: 2025-06-30

HGVS expressions

NM_206933.4:c.12505A>G
NM_206933.4(USH2A):c.12505A>G (p.Thr4169Ala)
NC_000001.11:g.215675406T>C
CM000663.2:g.215675406T>C
NC_000001.10:g.215848748T>C
CM000663.1:g.215848748T>C
NC_000001.9:g.213915371T>C
NG_009497.1:g.752991A>G
NG_009497.2:g.753043A>G
ENST00000307340.8:c.12505A>G
ENST00000674083.1:c.12505A>G
ENST00000307340.7:c.12505A>G
NM_206933.2:c.12505A>G
NM_206933.3:c.12505A>G

Likely Benign

Met criteria codes 1

BS1

Not Met criteria codes 6

PP3 PP4 PM3 BA1 BS2 BP4

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.12505A>G variant in USH2A is a missense variant predicted to cause substitution of threonine by alanine at amino acid 4169. The highest population minor allele frequency in gnomAD v4.1 is 0.003637 (273/75052 alleles) in the African/African-American population,

which is higher than the ClinGen HL VCEP threshold (>0.003]) for BS1, and therefore meets this criterion (BS1 met).The computational predictor REVEL gives a score of 0.207, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. (PP3 and BP4 not met). This variant has been observed in the homozygous state in at least six apparently healthy adults (GeneDx internal data, SCV000583079.4). This variant has also been observed with a co-occurring pathogenic variant, phase unknown, in three patients with retinitis pigmentosa/other retinal disease (Labcorp Genetics (formerly Invitae) SCV001039753.7). However, given its high allele frequency in the population and unknown phase with the co-occurring variant, PM3 was not applied. In summary, this variant has been classified as likely benign based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: BS1 (ClinGen Hearing Loss VCEP specifications version 2; 5/21/2025)

Met criteria codes

BS1	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.003637 (273/75052 alleles) in the African/African-American population, which is higher than the ClinGen HL VCEP threshold (>0.003]) for BS1, and therefore meets this criterion (BS1 met).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.207, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. (PP3 and BP4 not met).
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	✖	1.5 pts, not applied due to high allele frequency in the population and the co-occuring variants were of unknown phase.
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
BP4	✖	The computational predictor REVEL gives a score of 0.207, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. (PP3 and BP4 not met).

Curation History

Showing 1 to 3 of 3 rows