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Variant: NM_206933.4(USH2A):c.13808A>C (p.His4603Pro)

Version: 2.0

CA183350

178937 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 50f91390-6424-47ba-a587-3d70328e4353
Approved on: 2024/11/20
Published on: 2025/3/18

HGVS expressions

NM_206933.4(USH2A):c.13808A>C (p.His4603Pro)
NM_206933.4:c.13808A>C
NC_000001.11:g.215674103T>G
CM000663.2:g.215674103T>G
NC_000001.10:g.215847445T>G
CM000663.1:g.215847445T>G
NC_000001.9:g.213914068T>G
NG_009497.1:g.754294A>C
NG_009497.2:g.754346A>C
ENST00000307340.8:c.13808A>C
ENST00000674083.1:c.13808A>C
ENST00000307340.7:c.13808A>C
NM_206933.2:c.13808A>C
NM_206933.3:c.13808A>C

Likely Pathogenic

Met criteria codes 3

PP4 PM3_Strong PM2_Supporting

Not Met criteria codes 2

PP3 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.13808A>C (p.His4603Pro) variant in USH2A is a missense variant predicted to cause a substitution of histidine by a proline at amino acid 4603. The highest population minor allele frequency in gnomAD v4.1.0 is 0.00000084 (4/1179986 alleles) in the european non-finnish

population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.34, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. This variant has been detected in 1 proband with retinal disease and hearing loss (which was diagnosed at the age of 49 years old) in trans with a pathogenic variant by family testing (PMID: 28157192). Besides, this variant has been detected in 4 individuals with USH2A associated conditions which is highly specific for disease (PP4). All individuals were heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (c.2299del, p.(Glu767Serfs*21); c.5118G>A, p.(Trp1706*); c.2276G>T, p.(Cys759Phe) and c.5573-834A>G; PM3 3 points, Blueprint Genetics internal evidence SCV001239096.1) (PM3_Strong). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive USH2A condition (isolated RP) based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM2_P, PM3_Strong and PP4. (ClinGen Hearing Loss VCEP specifications version 2, 20.11.2024).

Met criteria codes

PP4	✔	This variant has been detected in 4 individuals with USH2A associated conditions which is highly specific for disease.
PM3_Strong	✔	Three PM3 points are given for the proband in Bravo-Gil 2017 and the four probands from Blueprints gentic clinical data
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00000084 (4/1179986 alleles) in the European non-Finnish population.

Not Met criteria codes

PP3	✖	REVEL score is 0.342.
BP4	✖	REVEL score is 0.342.

Curation History

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