

Variant: *NM_206933.3(USH2A):c.12574C>T (p.Arg4192Cys)*

Version: 2.0

CA1393449 [↗](#)

281818 (ClinVar) [↗](#)

Gene: USH2A ([HGNC:7399](#))

Condition: Usher syndrome ([MONDO:0019501](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 2c4d6b60-7250-4f03-8de9-0d25373a1521

Approved on: 2023/11/15

Published on: 2024/4/1

HGVS expressions

NM_206933.3(USH2A):c.12574C>T (p.Arg4192Cys)

NM_206933.3:c.12574C>T

NC_000001.11:g.215675337G>A

CM000663.2:g.215675337G>A

NC_000001.10:g.215848679G>A

CM000663.1:g.215848679G>A

NC_000001.9:g.213915302G>A

NG_009497.1:g.753060C>T

NG_009497.2:g.753112C>T

ENST00000307340.8:c.12574C>T

ENST00000674083.1:c.12574C>T

ENST00000307340.7:c.12574C>T

NM_206933.2:c.12574C>T

NM_206933.4:c.12574C>T

Likely Pathogenic

Met criteria codes **2**

PM3_Very Strong

PP4

Not Met criteria codes **4**

BP2

PP3

PM5

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.12574C>T variant in USH2A is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 4192 (p.Arg4192Cys). The highest population minor allele frequency in gnomAD v4.0 is 0.012% (144/1180032 alleles) in the European (non-

Finnish) population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL gives a score of 0.599, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. This variant was observed in at least 2 individuals with Usher syndrome and at least 10 individuals with isolated retinitis pigmentosa (RP) who were either homozygous or who carried a second P/LP variant in USH2A (PMID: 24516651, 27460420, 23940504, 27157150, 34906470, 24625443, 28127548, 28041643, 30190494, 29912909, 32176120, 33576794, 34781295, 36785559). At least one of these individuals was clinically evaluated and confirmed to have both sensorineural hearing loss and retinitis pigmentosa, which are highly specific for Usher syndrome (PP4; PMID: 27460420). Of note, an additional proband harbored this variant in cis with the known pathogenic p.Cys759Phe variant (PMID: 29912909), however the VCEP felt that the evidence supporting the pathogenicity of the p.Arg4192Cys variant outweighed this observation. Patients with this variant may present with either autosomal recessive (AR) Usher syndrome or with AR isolated RP. Isolated RP presentations are more common when the variant is seen with missense variants while Usher syndrome is more common when it is found with truncating variants. In summary, the clinical significance of this variant is likely pathogenic based on the ACMG/AMP criteria applied as specified by the Hearing Loss Expert Panel: PM3_VeryStrong, PP4. (ClinGen Hearing Loss VCEP specifications version 2, 11.15.2023)

Met criteria codes

PM3_Very Strong			The p.Arg4192Cys variant in USH2A was observed in at least 2 individuals with Usher syndrome and at least 10 individuals with isolated retinitis pigmentosa who were either homozygous or who carried a second P/LP variant in USH2A (PMID: 24516651, 27460420, 23940504, 27157150, 34906470, 24625443, 28127548, 28041643, 30190494, 29912909, 32176120, 33576794, 34781295, 36785559) .
PP4			1 proband was clinically evaluated and confirmed to have both sensorineural hearing loss and retinitis pigmentosa (PMID: 27460420).

Not Met criteria codes

BP2			Observed in cis with p.Cys759Phe, P/LP in ClinVar by 15 submitters. However, both missense variants were in trans with the p.Thr2812Metfs*17 variant.
PP3			The computational predictor REVEL gives a score of 0.599, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. Only 1 mammal (hedgehog) carries R>C substitution at this site. There is no predicted impact to splicing.
PM5			1 other variant in ClinVar (R4192H). Population data and computational predictors indicate that it is benign, however there are conflicting interpretations of pathogenicity. Only 1 assertion in HGMD for this variant is for Usher syndrome, and another variant in the gene was not identified in this family.
PM2			The highest population minor allele frequency in gnomAD v4 is 0.012% (144/1180032 alleles) in the European (non-Finnish) population (PM2_Supporting, BS1, and BA1 are not met).

Curation History 

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