

Variant: *NM_206933.3(USH2A):c.2081G>A (p.Cys694Tyr)*

Version: 1.1

CA1396311 [↗](#)

418533 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 25255e2d-61ae-4965-aa8b-19b4610689ce

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HGVS expressions

NM_206933.3(USH2A):c.2081G>A (p.Cys694Tyr)

NM_206933.3:c.2081G>A

NC_000001.11:g.216250989C>T

CM000663.2:g.216250989C>T

NC_000001.10:g.216424331C>T

CM000663.1:g.216424331C>T

NC_000001.9:g.214490954C>T

NG_009497.1:g.177408G>A

NG_009497.2:g.177460G>A

ENST00000307340.8:c.2081G>A

ENST00000674083.1:c.2081G>A

ENST00000307340.7:c.2081G>A

ENST00000366942.3:c.2081G>A

NM_007123.5:c.2081G>A

NM_206933.2:c.2081G>A

NM_007123.6:c.2081G>A

NM_206933.4:c.2081G>A

Likely Pathogenic

Met criteria codes **5**

PM3_Strong

PP3

PP4

PM2_Supporting

PM5

Evidence Links **0**

Expert Panel

Hearing Loss VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hearing Loss VCEP

The c.2081G>A in USH2A is a missense variant predicted to cause substitution of cysteine to tyrosine at amino acid 694 (p.Cys694Tyr). The highest population minor allele frequency in gnomAD v2.1.1 is 0.002% (2/113290) in the European (non-Finnish) sub-population which is below the threshold defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive Usher syndrome (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.92 (PP3). This variant has been detected in at least three probands with Usher syndrome whereby pathogenic or suspected-pathogenic variants were confirmed in trans in two individuals (2.5 PM3_Strong

points; PMID:28041643, Invitae Internal Data (SCV001372551.2)). Of the confirmed phase counts, the first harbored the p.Glu767SerfsTer21 variant and second harbored the p.Thr4425Met variant in USH2A (PMID:28041643, Invitae Internal Data). The third individual harbored the p.Cys3267Arg variant but phasing was not confirmed (Invitae Internal Data). At least one proband displayed features of hearing loss and retinitis pigmentosa, which is highly specific for USH2A and Usher syndrome (PP4; PMID: 28041643). Two missense variants, c.2081G>C (p.Cys694Ser) and c.2080T>A (p.Cys694Ser), in the same codon have been classified as likely pathogenic or pathogenic for AR Usher syndrome by two submitters in ClinVar (PM5; ClinVar Variation ID:1217348, 813246). In summary, this variant meets the criteria to be classified as likely pathogenic for AR Usher syndrome based on ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP; PM2_Supporting, PP3, PM3_Strong, PP4, PM5. (The ClinGen Hearing Loss VCEP Specifications Version 2; 06/27/2023).

Met criteria codes

PM3_Strong			This variant has been detected in at least three probands with Usher syndrome whereby pathogenic or suspected-pathogenic variants were confirmed in trans in two out of the three individuals (2.5 PM3_Strong points; PMID:28041643, Invitae Internal Data (SCV001372551.2)). Of the confirmed phase counts, the first harbored the p.Glu767SerfsTer21 variant and second harbored the p.Thr4425Met variant in USH2A (PMID:28041643, Invitae Internal Data). The third individual harbored the p.Cys3267Arg variant but phasing was not confirmed (Invitae Internal Data).
PP3			REVEL .92 No predicted splicing impact Evolutionarily conserved
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2_Supporting			Minor allele frequency of the variant is 2/113290 (0.002%) in European(non-Finnish) sub population in gnomAD v2.1.1 (PM2_Supporting met)
PM5			Two missense variants, c.2081G>C (p.Cys694Ser) and c.2080T>A (p.Cys694Ser), in the same codon have been classified as likely pathogenic or pathogenic for AR Usher syndrome by two submitters in ClinVar (PM5; ClinVar Variation ID:1217348, 813246).

Curation History

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