

Variant: *NM_206933.3(USH2A):c.11713C>T (p.Arg3905Cys)*

Version: 2.0

CA1393629 [↗](#)

236537 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 1358e892-e818-4d36-8c8f-962217401ae3

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HGVS expressions

NM_206933.3:c.11713C>T

NM_206933.3(USH2A):c.11713C>T (p.Arg3905Cys)

NC_000001.11:g.215728383G>A

CM000663.2:g.215728383G>A

NC_000001.10:g.215901725G>A

CM000663.1:g.215901725G>A

NC_000001.9:g.213968348G>A

NG_009497.1:g.700014C>T

NG_009497.2:g.700066C>T

ENST00000307340.8:c.11713C>T

ENST00000674083.1:c.11713C>T

ENST00000307340.7:c.11713C>T

NM_206933.2:c.11713C>T

NM_206933.4:c.11713C>T

Pathogenic

Met criteria codes 4

PM2_Supporting

PM3_Very Strong

PP3

PP4

Not Met criteria codes 1

PM5

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.11713C>T variant in USH2A is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 3905 (p.Arg3905Cys). The highest population minor allele frequency in gnomAD v4 is 0.007% (6/75036) in the African / African American

population, which meets the ClinGen Hearing Loss VCEP threshold ($\leq 0.007\%$) for PM2_Supporting. The computational predictor REVEL gives a score of 0.8, which is above the threshold of 0.7, evidence that correlates with impact to USH2A function (PP3). This variant has been detected in at least 6 individuals with Usher syndrome and at least 4 individuals with inherited retinal dystrophy. Of those individuals, 1 was homozygous and 7 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant. At least 1 of those were confirmed in trans by family testing (PM3_VeryStrong, PMID: 31877679, 25333064, 28559085, 24944099, 34781295, 36011402, 32531858, 36909829, 27208204, 37217489). At least one patient with this variant was diagnosed with Usher syndrome, which is highly specific for USH2A-related disorders (PP4, PMID: 31877679). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss Expert Panel: PM2_Supporting, PP3, PM3_VeryStrong, PP4. (ClinGen Hearing Loss VCEP specifications version 2; 10/16/2024).

Met criteria codes

PM2_Supporting			Present in 0.005026% (1/19896) of East Asian chromosomes in gnomAD v2. In v3, present in 0.03281% (1/3048) of South Asian chromosomes.
PM3_Very Strong			Observed in 6 individuals with Usher syndrome, 3 were compound het with a second Pathogenic or Likely pathogenic variant, but phase unknown (PMID: 31877679, 25333064, 25333064), 1 was homozygous (PMID: 34781295), and one was confirmed in trans with a pathogenic variant (PMID: 24944099), and one had a second variant of uncertain significance that was phase unknown (PMID: 36011402). Also observed in 4 individuals with retinal dystrophy or retinitis pigmentosa; 3 of whom had a second pathogenic or likely pathogenic variant phase unknown (PMID: 32531858, 36909829, 27208204), and 1 had a second pathogenic variant, but also had a third variant that was a VUS (PMID: 37217489). Total of 4.5 PM3 Points.
PP3			REVEL score 0.8. Not predicted to impact splicing. Cys is present in 1 other mammal in UCSC database (golden hamster).
PP4			1 proband with Usher syndrome type II PMID: 31877679

Not Met criteria codes

PM5			One other variant in this codon, c.11714G>A (p.Arg3905His), is classified as VUS by 1 submitter only.
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Curation History [↗](#)



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