

Variant: *NM_206933.3(USH2A):c.1859G>T (p.Cys620Phe)*

Version: 2.0

CA1396372 [↗](#)

549981 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: c6cc0a56-6e2d-4b2f-aa10-c7d1c4df0e45

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HGVS expressions

NM_206933.3(USH2A):c.1859G>T (p.Cys620Phe)

NM_206933.3:c.1859G>T

NC_000001.11:g.216289392C>A

CM000663.2:g.216289392C>A

NC_000001.10:g.216462734C>A

CM000663.1:g.216462734C>A

NC_000001.9:g.214529357C>A

NG_009497.1:g.139005G>T

NG_009497.2:g.139057G>T

ENST00000307340.8:c.1859G>T

ENST00000674083.1:c.1859G>T

ENST00000307340.7:c.1859G>T

ENST00000366942.3:c.1859G>T

NM_007123.5:c.1859G>T

NM_206933.2:c.1859G>T

NM_007123.6:c.1859G>T

NM_206933.4:c.1859G>T

Pathogenic

Met criteria codes **5**

PM2_Supporting

PM3_Very Strong

PP1

PP3

PP4

Not Met criteria codes **1**

PS3

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.1859G>T in USH2A is a missense variant predicted to cause a substitution of cysteine to phenylalanine at amino acid 620 (p.Cys620Phe) . The highest population minor allele frequency in gnomAD v2.1.1 is 0.004% (5/129062) 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 0.974 (PP3). This variant has been detected in at least four probands with other pathogenic or suspected-pathogenic variants confirmed in trans (4.0 PM3_Very Strong points; PMID: 22135276, 33089500, 36011334). The probands harbored these variants in USH2A: p.Trp1607*, p.Glu767Serfs*21, p.Cys759Phe, p.Gly3195*. At least one patient displayed features of hearing loss and retinitis pigmentosa, which is highly specific for USH2A and Usher syndrome (PP4; PMID: 22135276). The variant has been reported to segregate with AR Usher syndrome in one affected family member from one family (PP1; PMID: 36011334). In summary, this variant meets the criteria to be classified as pathogenic for AR Usher syndrome based on ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP; PM2_Supporting, PP3, PM3_Very Strong, PP4, PP1. (The ClinGen Hearing Loss VCEP Specifications Version 2; 06/27/2023).

Met criteria codes

PM2_Supporting			The minor allele frequency is 5/129062 (0.004%) in the European(non-Finnish) sub-population in gnomAD v2.1.1 (PM2_Supporting)
PM3_Very Strong			This variant has been detected in at least four probands with other pathogenic or suspected-pathogenic variants confirmed in trans (4.0 PM3_Very Strong points; PMID: 22135276, 33089500, 36011334). The probands harbored these variants in USH2A on the other allele: p.Trp1607*, p.Glu767Serfs*21, p.Cys759Phe, p.Gly3195*.
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL: .974
PP4			RP in Usher patients (PMID: 22135276)

Not Met criteria codes

PS3			Using a fusion peptide-based co-immunoprecipitation approach, we show that binding to fibronectin occurs at the LE domain of usherin. Recombinant LE domain-specific peptides were engineered that contained single amino acid substitutions corresponding to missense mutations found in humans with Usher syndrome type IIa. Only mutations in loop d of the LE domain abolished the ability of the LE domain to co-immunoprecipitate fibronectin. This is not a classic USH2A experiment and therefore was not counted. C620F failed to co-immunoprecipitate fibronectin from the tissue extracts. C620F maps to the d-loop of the predicted LE domain structure, strongly suggesting that this loop structure comprises the binding site for fibronectin C620F mutant peptides showed no evidence of competitive inhibition even at 400 molar excess of peptide. C620F disrupts the usherin/fibronectin interaction suggesting that the interaction is critical for stability and/or function of usherin in retinal basement membrane
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Curation History 

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