

Variant: *NM_206933.3(USH2A):c.5516T>A (p.Val1839Glu)*

Version: 2.0

CA10588918 [↗](#)

265979 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 949b8408-a95d-4d9c-836f-b9f8ae51effb

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HGVS expressions

NM_206933.3:c.5516T>A

NM_206933.3(USH2A):c.5516T>A (p.Val1839Glu)

NC_000001.11:g.216078145A>T

CM000663.2:g.216078145A>T

NC_000001.10:g.216251487A>T

CM000663.1:g.216251487A>T

NC_000001.9:g.214318110A>T

NG_009497.1:g.350252T>A

NG_009497.2:g.350304T>A

ENST00000307340.8:c.5516T>A

ENST00000674083.1:c.5516T>A

ENST00000307340.7:c.5516T>A

NM_206933.2:c.5516T>A

NR_125992.1:n.137-928A>T

NR_125993.1:n.136+5545A>T

NM_206933.4:c.5516T>A

Likely Pathogenic

Met criteria codes **3**

PM3_Strong

PP4

PM2_Supporting

Not Met criteria codes **1**

PP3

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.5516T>A variant in USH2A is a missense variant predicted to cause substitution of valine to glutamate at amino acid position 1839. The variant was absent from gnomAD v2.1.1 and present in 0.001549% (1/64578) of non-Finnish European chromosomes in gnomAD v3 (PM2_Supporting). Computational prediction tools and conservation analyses do not provide strong support for or against an impact to the protein. This variant has been detected in at least 4 individuals (2 with Usher syndrome and 2 with isolated retinitis pigmentosa) (total of 2.5 PM3 points, PM3_Strong). One individual with Usher syndrome was assumed to be compound heterozygous with a pathogenic

c.2299del variant, but phase unknown (VCV000002351.78; PMID: 26927203). The other two individuals had retinitis pigmentosa and were assumed compound heterozygous with pathogenic p.(Cys759Phe) variant (VCV000002356.89; PMID: 26927203; PMID: 34203967). One patient displayed both retinal degradation and sensorineural hearing loss, features highly specific for USH2A (PP4). Patients with this variant may present with either Usher syndrome or with 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. ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss Expert Panel: PM2_Supporting, PM3_Strong, PP4 (VCEP specifications version 2; 10.18.2023).

Met criteria codes

PM3_Strong			2.5 PM3 points from 4 individuals (2 with Usher Syndrome and 2 with reinitis pigmentosa) who were assumed compound heterozygous with pathogenics variant. Reports from Neuhaus et al; Pierrache et al; Janine Reurink et al.
PP4			1 patient proband had a diagnosis of retinal degeration and sensorineural hearing loss.
PM2_Supporting			Absent from gnomAD v2. Present in 0.001470% (1/68036) of non-Finnish European chromosomes in gnomAD v3.

Not Met criteria codes

PP3			REVEL score 0.556. Not present in any animals in UCSC database. Splicing is not predicted to be impacted using Alamut.
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Curation History

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