Variant: NM_206933.4(USH2A):c.6446C>A (p.Pro2149Gln)

Version: 2.0

CA354063

224753 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: ba64373e-1f84-4b4e-9c18-a3c165795d50
Approved on: 2025-04-16
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HGVS expressions

NM_206933.4:c.6446C>A
NM_206933.4(USH2A):c.6446C>A (p.Pro2149Gln)
NC_000001.11:g.216000442G>T
CM000663.2:g.216000442G>T
NC_000001.10:g.216173784G>T
CM000663.1:g.216173784G>T
NC_000001.9:g.214240407G>T
NG_009497.1:g.427955C>A
NG_009497.2:g.428007C>A
ENST00000307340.8:c.6446C>A
ENST00000674083.1:c.6446C>A
ENST00000307340.7:c.6446C>A
NM_206933.2:c.6446C>A
NM_206933.3:c.6446C>A

Uncertain Significance

Met criteria codes 3

PP4 PM3 PM2_Supporting

Not Met criteria codes 6

PS1 PP3 PM5 BA1 BS1 BP4

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 NM_206933.4:c.6446C>A variant in the USH2A gene is a missense variant predicted to cause the substitution of proline by glutamine at amino acid 2149 (p.Pro2149Gln). The minor allele frequency of this variant in gnomAD v.4.1.0 was 0.00059% (7/1179718 alleles) in the

European (non-Finnish) population meeting PM2_Supporting. The REVEL computational prediction analysis tool produced a score of 0.355, which doesn't meet either of the thresholds necessary to apply PP3/BP4. It has been detected with another suspected pathogenic variant in two patients with Usher syndrome type 2, of which one patient displayed hearing loss with an onset in the first decade and retinitis pigmentosa with an onset at 22y.o, which is specific for Usher syndrome (PM3, PP4; PMIDs: 26872967, 29074561, 32176120, 31836858). In summary, this variant meets criteria to be classified as variant of uncertain significance for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied as specified by the ClinGen Hearing Loss Expert Panel: PM3, PM2_Supporting, PP4 (ClinGen Hearing Loss VCEP specifications version 2; 4/16/2025).

Met criteria codes

PP4	✔	At least one patient with this variant displayed hearing loss with an onset in the first decade and retinitis pigmentosa with an onset at 22y.o, which is specific for Usher type II syndrome (PMID : 32176120).
PM3	✔	This variant has been detected in 2 individuals referred as Usher syndrome. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and 1 of those were confirmed in trans by parental testing (PMID: 26872967, 29074561, 32176120, 31836858). This variant has also been detected in an individual referred as isolated retinitis pigmentosa and was not scored since hearing loss or precision about their hearing status was not reported. This patient were compound heterozygous for this variant and a pathogenic alteration (PMID: 38219857; 28041643).
PM2_Supporting	✔	The minor allele frequency of this variant in gnomAD v.4.1.0 was 0.00059% (7/1179718 alleles) in the European (non-Finnish) population meeting PM2_Supporting.

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	The REVEL computational prediction analysis tool produced a score of 0.355, which doesn't meet either of the thresholds necessary to apply PP3/BP4.
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	The minor allele frequency of this variant in gnomAD v.4.1.0 was 0.00059% (7/1179718 alleles) in the European (non-Finnish) population meeting PM2_Supporting.
BS1	✖	The minor allele frequency of this variant in gnomAD v.4.1.0 was 0.00059% (7/1179718 alleles) in the European (non-Finnish) population meeting PM2_Supporting.
BP4	✖	The REVEL computational prediction analysis tool produced a score of 0.355, which doesn't meet either of the thresholds necessary to apply PP3/BP4.

Curation History

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