Variant: NM_206933.3(USH2A):c.14219C>A (p.Ala4740Asp)

Version: 2.0

CA1393090

429215 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2c976ce7-47ec-4c6f-b6ff-5356baa40521
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HGVS expressions

NM_206933.3:c.14219C>A
NM_206933.3(USH2A):c.14219C>A (p.Ala4740Asp)
NC_000001.11:g.215650716G>T
CM000663.2:g.215650716G>T
NC_000001.10:g.215824058G>T
CM000663.1:g.215824058G>T
NC_000001.9:g.213890681G>T
NG_009497.1:g.777681C>A
NG_009497.2:g.777733C>A
ENST00000307340.8:c.14219C>A
ENST00000674083.1:c.14219C>A
ENST00000307340.7:c.14219C>A
NM_206933.2:c.14219C>A
NM_206933.4:c.14219C>A

Pathogenic

Met criteria codes 3

PP4 PM3_Very Strong PM2_Supporting

Not Met criteria codes 3

PP3 PM5 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 c.14219C>A (p.Ala4740Asp) variant in USH2A is a missense variant predicted to cause a substitution of alanine by aspartic acid at amino acid 4740. The highest population minor allele frequency in gnomAD v4.0.0 is 0.006102% (72/1180006) in the European (Non-Finish)

population, which is lower than the ClinGen Hearing Loss VCEP threshold (≤0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.309, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function. This variant has been detected in at least 2 individuals with Usher syndrome, and in at least 5 individuals with Retinitis Pigmentosa (RP) (4 PM3 pts). The two individuals with Usher syndrome were compound heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (p.Arg737*, p.Ser1849fs; PMIDs: 33576794, 38465142). At least one patient with this variant displayed retinitis pigmentosa and sensorineural bilateral hearing loss, which is highly specific for Usher syndrome (PP4, PMID: 33576794). Of the individuals with RP, four individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (p.Ser1849fs, p.Arg737*, c.7595-2144A>G, p.Arg4192Cys; PMIDs: 30718709, 34781295, 32531858). One individual was compound heterozygous and confirmed in trans by parental testing for the variant and a pathogenic or likely pathogenic variant (p.Arg1653*; PMIDs: 34781295) (PM3_VeryStrong). Patients with this variant may present with either autosomal recessive (AR) Usher syndrome or with AR 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, 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 VCEP (PM2_Supporting, PM3_VeryStrong, PP4; Version 2; 4/17/24).

Met criteria codes

PP4	✔	At least one patient with this variant displayed retinitis pigmentosa and sensorineural bilateral hearing loss, which is highly specific for Usher syndrome (PP4, PMID: 33576794).
PM3_Very Strong	✔	This variant has been detected in at least 2 individuals with Usher syndrome, and in at least 5 individuals with Retinitis Pigmentosa (RP) (4 PM3 pts). The two individuals with Usher syndrome were compound heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (p.Arg737*, p.Ser1849fs; PMIDs: 33576794, 38465142). At least one patient with this variant displayed retinitis pigmentosa and sensorineural bilateral hearing loss, which is highly specific for Usher syndrome (PP4, PMID: 33576794). Of the individuals with RP, four individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (p.Ser1849fs, p.Arg737*, c.7595-2144A>G, p.Arg4192Cys; PMIDs: 30718709, 34781295, 32531858). One individual was compound heterozygous and confirmed in trans by parental testing for the variant and a pathogenic or likely pathogenic variant (p.Arg1653*; PMIDs: 34781295) (PM3_VeryStrong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.0.0 is 0.006102% (72/1180006) in the European (Non-Finish) population, which is lower than the ClinGen Hearing Loss VCEP threshold (≤0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.309, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function.
PM5	✖	Currently no other variants at this codon in ClinVar.
BP4	✖	The computational predictor REVEL gives a score of 0.309, which is neither above nor below the thresholds predicting a damaging or benign impact on USH2A function.

Curation History

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