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Variant: NM_206933.4(USH2A):c.12874A>G (p.Asn4292Asp)

Version: 2.0

CA143304

48409 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: inherited retinal dystrophy (MONDO:0019118)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3462992d-0234-401e-b823-3d37b89833bd
Approved on: 2024/5/15
Published on: 2024/7/2

HGVS expressions

NM_206933.4(USH2A):c.12874A>G (p.Asn4292Asp)
NM_206933.4:c.12874A>G
NC_000001.11:g.215675037T>C
CM000663.2:g.215675037T>C
NC_000001.10:g.215848379T>C
CM000663.1:g.215848379T>C
NC_000001.9:g.213915002T>C
NG_009497.1:g.753360A>G
NG_009497.2:g.753412A>G
ENST00000307340.8:c.12874A>G
ENST00000674083.1:c.12874A>G
ENST00000307340.7:c.12874A>G
NM_206933.2:c.12874A>G
NM_206933.3:c.12874A>G

Likely Pathogenic

Met criteria codes 3
PM3_Strong PP1 PP3

Not Met criteria codes 1
PM2

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*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.12874A>G variant in USH2A is a missense variant predicted to cause substitution of asparagine by aspartic acid at amino acid 4292 (p.Asn4292Asp). The highest population frequency in gnomAD v4.1.0 is 0.02% (20/86258 alleles) in the South Asian population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL gives a score of 0.707, which is above the threshold of

0.7, evidence that correlates with impact to USH2A function (PP3). This variant has been identified in at least 6 individuals with apparently isolated retinal dystrophy. One individual was homozygous, one was heterozygous for a second variant of uncertain significance, three had a second pathogenic variant with phase unknown, and one harbored a second pathogenic variant confirmed in trans (2 points, PM3_Strong, PMID: 28041643, 25133751, 37322672, Invitae Internal evidence SCV001403886.5, Blueprint Genetics internal evidence SCV001240918.1). The variant has been reported to segregate with retinal dystrophy in 1 affected family member from 1 family (PP1; PMID: 25133751). Of note, hearing loss was not reported in any of these individuals, indicating that this variant is likely causative for isolated retinal dystrophy and not Usher syndrome. In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive inherited retinal dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PP3, PM3_Strong, PP1. (Hearing loss VCEP specifications version 2; 05.15.2024).

Met criteria codes

PM3_Strong	✔	PMID: 25133751, 28041643, 37322672, Invitae Internal evidence SCV001403886.5, Blueprint Genetics internal SCV001240918.1
PP1	✔	Downgraded from PP1_Moderate. The variant segregated in 1 affected family member from Watson 2014 PMID: 25133751. Though there are 2 affected sibs, only 1 had DNA available.
PP3	✔	REVEL: 0.707

Not Met criteria codes

PM2	✖	The highest population frequency in gnomAD v4.1.0 is 0.02% (20/86258 alleles) in the South Asian population (PM2_Supporting, BS1, and BA1 are not met).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_206933.4(USH2A):c.12874A>G (p....	Likely Pathogenic	Inherited Retinal Dystrophy	2024-07-02	2.0	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	USH2A
View	NM_206933.4(USH2A):c.12874A>G (p....	Uncertain Significance	Usher Syndrome	2020-07-28	1.0	-	USH2A

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