Variant: NM_206933.3(USH2A):c.5012G>A (p.Gly1671Asp)

Version: 2.0

CA185105

179773 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: inherited retinal dystrophy (MONDO:0019118)
Inheritance Mode: Autosomal recessive inheritance
UUID: 24df34e2-4a6c-48b7-bc9a-24a20326902c
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HGVS expressions

NM_206933.3:c.5012G>A
NM_206933.3(USH2A):c.5012G>A (p.Gly1671Asp)
NC_000001.11:g.216084853C>T
CM000663.2:g.216084853C>T
NC_000001.10:g.216258195C>T
CM000663.1:g.216258195C>T
NC_000001.9:g.214324818C>T
NG_009497.1:g.343544G>A
NG_009497.2:g.343596G>A
ENST00000307340.8:c.5012G>A
ENST00000674083.1:c.5012G>A
ENST00000307340.7:c.5012G>A
ENST00000463147.1:n.256G>A
ENST00000481786.1:n.254G>A
NM_206933.2:c.5012G>A
NR_125992.1:n.266-1869C>T
NR_125993.1:n.137-1869C>T
NM_206933.4:c.5012G>A

Pathogenic

Met criteria codes 3

PP1_Strong PP3 PM3_Very Strong

Not Met criteria codes 3

BP5 PP4 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.5012G>A variant in USH2A is a missense variant predicted to cause substitution of glycine by aspartic acid at amino acid 1671 (p.Gly1671Asp). The highest population minor allele frequency in gnomAD v4 is 0.04% (51/91074 alleles) in the South Asian population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL gives a score of 0.906, which is above the threshold of 0.7, evidence that correlates with impact to USH2A function (PP3). This variant has been detected in at least 10 individuals with retinitis pigmentosa or inherited retinal disease. Of those individuals, 9 were homozygous and 1 was compound heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (c.4251+1G>T, 5 PM3 points, PMID:26667666, 32581362, 33749171, 38219857, PM3_VeryStrong). Internal evidence from one laboratory indicates that this variant has been observed in trans with a likely pathogenic missense variant in an individual with optic neuropathy, night blindness, and sensorineural hearing loss and homozygous in one individual with hearing loss and hyperopia (Personal communication, SCV001789135.4). This suggests that there may be phenotypic variability with some individuals presenting with isolated retinal dystrophy, and some presenting with hearing loss and signs and/or symptoms of retinal dystrophy. Of note, many of these individuals were of South Asian ancestry, consistent with the population evidence from gnomAD (PMID:38219857). The variant has been reported to segregate with inherited retinal disease in 3 affected family members from 2 families (PP1_Strong; PMID: 38219857). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive USH2A-related inherited retinal dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PP3, PM3_VeryStrong, PP1_Strong. (ClinGen Hearing Loss VCEP specifications version 2, 02.27.2024).

Met criteria codes

PP1_Strong	✔	Two families reported in PMID: 38219857. Scored 3 AR segregations based on the supplemental information. Though I will note we don't fully know the relationship or confirmation that parents are het only. However, Andrea/Marina discussed over slack and agreed to add this evidence to classify as pathogenic (otherwise variant was a VUS).
PP3	✔	REVEL score 0.906. Not predicted to impact splicing by Alamut. No animals in UCSC database have an alternate amino acid at this site.
PM3_Very Strong	✔	UPDATED SCORING SUMMARIZED HERE: https://docs.google.com/presentation/d/1cXGQOS8ttWBu3DRrsrsnXxonPkt_ubSJ0yi8LHJ-p8E/edit#slide=id.g2b9f26a1ae1_0_33 PRIOR SCORING FROM 2019: -LMM internal data: identified in 1 individual with sloping moderately-severe SNHL with RP. Family history of isolated HL and RP. Other USH2A variant was c.12877G>A (p.Gly4293Ser) [VUS]. Also compound het for RDX c.97-10_97-8delTGT [LB], CDH23 c.429+4G>A [VUS/LB], and WFS1 c.2414G>A (p.Arg805Gln) [VUS]. Of note, Wolfram syndrome can also cause SNHL and optic atrophy. No PM3 points since other variant is a VUS and phase is unknown. -Also identified in 2 Indian individuals with Usher syndrome (Le Quesne Stabej). Personal communications to LMM indicate 1 individual had 2 additional variants in USH2A; a second variant was not identified in the other individual (0 PM3 points) -Also identified in 2 SAS individuals with RP (Carss) and 2 other individuals with RP who were homozygous for the variant (Ge)

Not Met criteria codes

BP5	✖	Option to apply because of variant in WFS1
PP4	✖	1 patient from LMM internal data with moderately-severe SNHL with RP. However PP4 was not applied since the proband also carried the c.2414 (p.Arg805Gln) variant in WFS1, which has been definitively associated with Wolfram-like syndrome, an AD disease that can result in optic atrophy and progressive HL.
PM2	✖	gnomAD v4 - FAF 0.04% (51/91074) in South Asian chromosomes, does not meet PM2_Supporting (<0.007%) or BS1 (≥0.3%)

Curation History

ng 1 to 2 of 2 rows