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

Version: 1.0

CA185105

179773 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
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

Uncertain Significance

Met criteria codes 2

PM2_Supporting **PP3**

Not Met criteria codes 3

BP5 **PP4** **PM3**

Evidence Links 3

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.5012G>A (p.Gly1671Asp) variant in USH2A is present in 0.0392% (12/30616) of South Asian chromosomes in gnomAD, which is a low enough frequency to apply PM2_Supporting based on the thresholds defined by the Hearing Loss Variant Curation Expert Panel. Computational prediction tools and conservation analyses suggest that the p.Gly1671Asp variant may impact the protein (PP3). This

variant was identified in 3 individuals with Usher syndrome harboring this variant; however, either variants in other alleles were not identified or alternate mechanisms of disease were present (LMM internal data, SCV000206290.5; PMID: 22135276). The p.Gly1671Asp variant was also found in four individuals with retinitis pigmentosa, but not Usher syndrome (PMID: 28041643, 26667666). In summary, the clinical significance of this variant is uncertain. ACMG/AMP Criteria applied: PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting	✓	Present in 0.0392% (12/30616) of South Asian chromosomes in gnomAD.
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.

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.
PM3	✗	-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) PubMed:26667666 PubMed:28041643 PubMed:22135276

Curation History

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