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Variant: NM_000260.4(MYO7A):c.401T>A (p.Ile134Asn)

Version: 2.0

CA278663

43230 (ClinVar)

Gene: MYO7A (HGNC:4647)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 28c29ee7-31d4-4833-afbd-15bf5b29aa05
Approved on: 2024/9/18
Published on: 2024/9/30

HGVS expressions

NM_000260.4(MYO7A):c.401T>A (p.Ile134Asn)
NM_000260.4:c.401T>A
NC_000011.10:g.77156022T>A
CM000673.2:g.77156022T>A
NC_000011.9:g.76867068T>A
CM000673.1:g.76867068T>A
NC_000011.8:g.76544716T>A
NG_009086.1:g.32759T>A
NG_009086.2:g.32777T>A
ENST00000409709.9:c.401T>A
ENST00000409619.6:c.368T>A
ENST00000409709.7:c.401T>A
ENST00000409893.5:c.401T>A
ENST00000458637.6:c.401T>A
ENST00000620575.4:c.401T>A
NM_000260.3:c.401T>A
NM_001127179.2:c.401T>A
NM_001127180.1:c.401T>A
NM_001127180.2:c.401T>A
NM_001369365.1:c.368T>A

Pathogenic

Met criteria codes 5

PP1 PP3 PP4 PM2_Supporting PM3_Very Strong

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.401T>A (p.Ile134Asn) is a missense variant in MYO7A predicted to cause a substitution of isoleucine to asparagine at amino acid 134. The filtering allele frequency (the lower threshold of the 95% CI of 60/1179894) of this variant is 0.004019% in the European (non-Finnish) population which meets the threshold (≤0.00007, 0.007%) defined by the ClinGen Hearing Loss Expert Panel for PM2_Supporting for autosomal recessive Usher syndrome (PM2_Supporting). The REVEL computational prediction tool produced a score of 0.938, which is above the threshold necessary to apply PP3 (PP3). This variant has been detected in 7 probands with Usher syndrome. For 2 of those probands, pathogenic variants (c.19-1G>A and p.Gly214Arg) were observed in trans, and in the other 5 probands, a pathogenic variant was observed with unknown phase (4.5 points, PM3_Very Strong, PMIDs: 25468891, 26969326, 33089500, 37510321, Partners LMM Internal Data ClinVar SCV000059786.6). The variant has been reported to segregate with hearing loss in one affected family member (PP1, Partners LMM Internal Data ClinVar SCV000059786.6). At least one patient with this variant displayed features of sensorineural hearing loss and retinitis pigmentosa, which are consistent for Usher syndrome, a condition highly specific for MYO7A (PP4, Partners LMM Internal Data ClinVar SCV000059786.6). In summary, this variant meets 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 Expert Panel (PM3_Very Strong, PM2_Supporting, PP1, PP3, PP4). (ClinGen Hearing Loss VCEP specifications version 2; 9/18/2024).

Met criteria codes

PP1	✔	2 sisters from LMM segregated with two MYO7A variants.
PP3	✔	The REVEL score is 0.938 and there is no impact to splicing. The residue is conserved in all vertebrates in the UCSC browser.
PP4	✔	The 2 sisters both had SNHL and RP, which are highly specific for Usher syndrome.
PM2_Supporting	✔	The Grpmax FAF in gnomAD v4.1 is 0.004019% in the European (non-Finnish) population which is below the threshold defined by the ClinGen HL EP for PM2 Supporting (≤0.00007 (0.007%)) for autosomal recessive conditions (PM2_S)
PM3_Very Strong	✔	A total of 4.5 PM3 points lead to a very strong classification. 7 probands with Usher syndrome were include in this curation. For 2 of those probands, pathogenic variants (c.19-1G>A and Gly214Arg) were observed in trans, and in the other 5 probands, a pathogenic variant was observed with unknown and/or unspecified phase (PM3_Very Strong, PMIDs: 25468891, 26969326, 33089500, 37510321, Partners LMM Internal Data ClinVar SCV000059786.6).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000260.4(MYO7A):c.401T>A (p.Ile...	Pathogenic	Usher Syndrome	2024-09-30	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	MYO7A
View	NM_000260.4(MYO7A):c.401T>A (p.Ile...	Likely Pathogenic	Usher Syndrome	2020-11-02	1.0	-	MYO7A

Showing 1 to 2 of 2 rows

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