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Variant: NM_000260.4(MYO7A):c.5618G>A (p.Arg1873Gln)

Version: 1.0

CA278687

43292 (ClinVar)

Gene: MYO7A (HGNC:4647)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: ba742d08-69a6-4fa1-b737-dbd16b210ece
Approved on: 2019-11-26
Published on: 2019-11-26

HGVS expressions

NM_000260.4:c.5618G>A
NM_000260.4(MYO7A):c.5618G>A (p.Arg1873Gln)
NC_000011.10:g.77205599G>A
CM000673.2:g.77205599G>A
NC_000011.9:g.76916644G>A
CM000673.1:g.76916644G>A
NC_000011.8:g.76594292G>A
NG_009086.1:g.82335G>A
NG_009086.2:g.82354G>A
ENST00000409709.9:c.5618G>A
ENST00000670577.1:c.3445G>A
ENST00000409619.6:c.5471G>A
ENST00000409709.7:c.5618G>A
ENST00000458169.2:c.3044G>A
ENST00000458637.6:c.5504G>A
ENST00000481328.7:n.3154G>A
ENST00000605744.1:n.239G>A
NM_000260.3:c.5618G>A
NM_001127180.1:c.5504G>A
NM_001127180.2:c.5504G>A
NM_001369365.1:c.5471G>A

Pathogenic

Met criteria codes 6

PP1 PP3 PP4 PM3_Strong PM2_Supporting PM5

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 allele frequency of the p.Arg1873Gln variant in the MYO7A gene is 0.008% (2/24854) of European chromosomes by gnomAD, which is a low enough frequency to apply PM2_Supporting based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2_Supporting). This variant has been detected in 2 probands with hearing loss and 2 probands with Usher syndrome. For 2 of those probands, a pathogenic or suspected-pathogenic variant was observed in trans, for 1 proband a pathogenic or suspected-pathogenic was suspected in trans, and for 1 of the probands, a rare variant of uncertain significance was observed in trans (PM3_Strong; PMID:23208854, 28000701, 29196752, Partners LMM internal data SCV000059849.6). The variant has been reported to segregate with hearing loss in one affected family member (PP1, Partners LMM internal data SCV000059849.6). A different pathogenic missense variant (p.Arg1873Trp) has been previously identified at this codon of MYO7A which may indicate that this residue is critical to the function of the protein (PM5; p.Arg1873Trp ClinVar Variation ID 43291). The REVEL computational prediction analysis tool produced a score of 0.936, which is above the threshold necessary to apply PP3. At least one of the above patients with the variant in this gene displayed features of Usher syndrome (PP4; Partners LMM internal data SCV000059849.6). 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 Hearing Loss Expert Panel: PM3_Strong, PM2_Supporting, PM5, PP1, PP3, PP4.

Met criteria codes

PP1	✔	This variant was identified with in two siblings with Usher syndrome. (LMM internal data SCV SCV000059849.6)
PP3	✔	The REVEL score is 0.936, which is higher than our cutoff for pathogenicity of 0.7. The variant is entirely conserved.
PP4	✔	This variant has been identified in 2 siblings with Congenital profound sensorineural hearing loss with retinitis pigmentosa (LMM internal data SCV SCV000059849.6)
PM3_Strong	✔	There are 4 compound het observations: 2 with a known path/lp variant in trans (Schrauwen 2013 and Zazo Seco 2017, 2 pts), one with a VUS in trans (Baux 2017, 0.25 pts), and one with a LP/P variant phase unknown (LMM internal data SCV000059849.6, 0.5pts) 2.75pts total, Strong. PubMed:28000701 PubMed:16963483 PubMed:29196752
PM2_Supporting	✔	Variant is present in v2: 2/24854 European alleles 0.008% v3: 1/10472 European alleles 0.0095%
PM5	✔	The p.Arg1873Trp variant is classified as a two star likely pathogenic/pathogenic variant in ClinVar. It has been observed in either the compound heterozygous or homozygous state in 5 patients with Usher syndrome.

Curation History

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