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Variant: NM_000260.3(MYO7A):c.3503G>A (p.Arg1168Gln)

Version: 1.0

CA184505

179479 (ClinVar)

Gene: MYO7A (HGNC:4647)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: b16ffcc3-3e9d-4890-aca5-e535579a2453
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HGVS expressions

NM_000260.3:c.3503G>A
NM_000260.3(MYO7A):c.3503G>A (p.Arg1168Gln)
NC_000011.10:g.77184715G>A
CM000673.2:g.77184715G>A
NC_000011.9:g.76895760G>A
CM000673.1:g.76895760G>A
NC_000011.8:g.76573408G>A
NG_009086.1:g.61451G>A
NG_009086.2:g.61470G>A
ENST00000409709.9:c.3503G>A
ENST00000409893.6:c.1568G>A
ENST00000670577.1:c.1344G>A
ENST00000409619.6:c.3470G>A
ENST00000409709.7:c.3503G>A
ENST00000409893.5:c.3503G>A
ENST00000458169.2:c.1046G>A
ENST00000458637.6:c.3503G>A
ENST00000467137.1:n.30G>A
ENST00000481328.7:n.1046G>A
ENST00000620575.4:c.3500+12G>A
NM_001127179.2:c.3503G>A
NM_001127180.1:c.3503G>A
NM_000260.4:c.3503G>A
NM_001127180.2:c.3503G>A
NM_001369365.1:c.3470G>A

Pathogenic

Met criteria codes 5

PP3 PP4 PM5 PM2 PM3_Strong

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.3503G>A (p.Arg1168Gln) variant in MYO7A has been detected in at least 4 probands with Usher syndrome. For two of those probands, a pathogenic or suspected-pathogenic variants was observed in trans, and in one individual, the variant was observed with a pathogenic or suspected-pathogenic variant, but it was unclear if phasing was performed (PM3_Strong, PP4; PMID:25404053, 27460420, 28944237). The allele frequency of this variant is 0.004%% (1/26850) of South Asian chromosomes by gnomAD, which is a low enough frequency to apply PM2 based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2). The c.3503G>A (p.Arg1168Gln) variant is located in the last base of the exon, which is part of the 5' consensus sequence, and computational tools suggest an impact to splicing. Furthermore, tThe REVEL computational prediction analysis tool produced a score of 0.9, which is above the threshold necessary to apply PP3. A different likely pathogenic or suspected-pathogenic variant at the same nucleotide (c.3503G>C, Arg1168Pro) has been previously identified in an individual with Usher syndrome who was compound heterozygous for a second pathogenic truncating variant (PMID: 16470552). In addition, a minigene assay demonstrated that the 3503G>C variant led to skipping of exon 27 (PMID: 20052763) suggesting that variants that alter the c.3503G nucleotide may cause abnormal splicing (PM5_Supporting). In summary, this variant meets criteria to be classified as likely pathogenic for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PM3_Strong, PP4, PM2, PP3, PM5_Supporting.

Met criteria codes

PP3	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✔	Bonnet 2016, patient with USH1
PM5	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✔	0.004%, 1/26850 of S. Asian chr in gnomad
PM3_Strong	✔	1 point from Aparisi 2014 (Gln1798X / Arg1168Gln, variants likely phased). 0.5 points from Bonnet 2016 (p.Arg1168Gln / exon 46 del (in frame), variants phased), 0.5 points from Neuhaus (Arg1168Gln / 6025delG, unclear if phased). Patient with USH type 1 compound het for MYO7A:c.3503G4A (p.Arg1168Gln)+deletion of exon 46, and was heterozygous for USH2A:c.2299delG (p.Glu767Serfs*21). According to entry in LOVD USHbases, deletion of exon 46 is c.6238-?_6354+?del (in frame exon deletion) PubMed:27460420 Arg1168Gln was identified in 2 patients with Usher syndrome. RP-807 harbored Arg1168Gln / Leu1839Pro (vus). RP-1924 harbored Gln1798X / Arg1168Gln. Both patients were reported to have segregation analysis performed in family members. PubMed:25404053 Two patients with atypical usher syndrome. Patient 13: Arg1168Gln / 6025delG. Patient 14: Arg1168Gln / Leu1839Pro (vus). PubMed:28944237

Curation History

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