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Version: 1.0

CA1563057

2429109 (ClinVar)

Gene: OTOF (HGNC:9381)
Condition: autosomal recessive nonsyndromic deafness 9 (MONDO:0010986)
Inheritance Mode: Autosomal recessive inheritance
UUID: 42cb25c9-af9e-4a41-8e82-25e04ca787fc
Approved on: 2022-08-03
Published on: 2022-08-03

HGVS expressions

NM_194323.3:c.2447G>A
NC_000002.12:g.26465723C>T
CM000664.2:g.26465723C>T
NC_000002.11:g.26688591C>T
CM000664.1:g.26688591C>T
NC_000002.10:g.26542095C>T
NG_009937.1:g.97976G>A
ENST00000272371.7:c.4748G>A
ENST00000339598.8:c.2447G>A
ENST00000402415.8:c.2507G>A
ENST00000272371.6:c.4748G>A
ENST00000338581.10:c.2447G>A
ENST00000339598.7:c.2447G>A
ENST00000402415.7:c.2678G>A
ENST00000403946.7:c.4748G>A
ENST00000464574.1:n.497G>A
NM_001287489.1:c.4748G>A
NM_004802.3:c.2447G>A
NM_194248.2:c.4748G>A
NM_194322.2:c.2678G>A
NM_194323.2:c.2447G>A
NM_001287489.2:c.4748G>A
NM_004802.4:c.2447G>A
NM_194248.3:c.4748G>A
NM_194322.3:c.2678G>A

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3 PM5 PM2_Supporting

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 OTOF and MYO15A Version 1*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.4748G>A variant in OTOF is a missense variant predicted to cause substitution of arginine by histidine at amino acid 1583. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006152 (1/16254 alleles) in the African/African American population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.912, which is above the threshold of 0.7, evidence that correlates with impact to OTOF function (PP3). Another missense variant c.4747C>T (p.R1583C) (PMID:26818607, 31589614, 32747562, 33724713, 34426522, ClinVar Variation ID:402270) in the same codon has been classified as pathogenic/likely pathogenic for autosomal recessive nonsyndromic hearing loss in ClinVar (PM5). At least one patient with this variant and compound heterozygous for the c.2215-1G>C variant displayed auditory neuropathy spectrum disorder (ANSD), which is highly specific for ANSD (PP4, PMID:24001616). This variant has been detected in at least 1 individual with ANSD, who was compound heterozygous for the variant and a pathogenic or likely pathogenic variant were confirmed in trans by family testing (c.2215-1G>C, 1 PM3 point, PMID:24001616). Additional compound heterozygous cases with variants c.5816G>A (p.R1939Q), c.3515G>A (p.R1172Q), and c.2523+1G>T (PMIDs: 24053799, 31095577, 31827501 respectively) were also seen, but excluded from scoring due to less scorable evidence. In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive nonsyndromic hearing loss based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM2_P, PP3, PM5, PP4, PM3 (ClinGen Hearing Loss VCEP specifications version 2; 7/21/2022).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.912, which is above the threshold of 0.7, evidence that correlates with impact to OTOF function (PP3).
PP4	✔	At least one patient was compound heterozygous for this variant and displayed auditory neuropathy spectrum disorder (ANSD), which is highly specific for ANSD (PP4, PMID:23208854).
PM3	✔	This variant has been detected in at least 1 individual with ANSD, who was compound heterozygous for the variant and a pathogenic or likely pathogenic variant were confirmed in trans by family testing (c.2215-1G>C, 1 PM3 point, PMID:24001616). Additional compound heterozygous cases with variants c.5816G>A (p.R1939Q), c.3515G>A (p.R1172Q), and c.2523+1G>T (PMIDs: 24053799, 31095577, 31827501 respectively) were also seen, but excluded from scoring due to less scorable evidence.
PM5	✔	Another missense variant c.4747C>T (p.R1583C) (PMID:26818607, 31589614, 32747562, 33724713, 34426522, ClinVar Variation ID:402270) in the same codon has been classified as pathogenic/likely pathogenic for autosomal recessive nonsyndromic hearing loss in ClinVar (PM5).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006152 (1/16254 alleles) in the African/African American population, which is lower than the ClinGen Hearing Loss VCEP threshold (<0.00007) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

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