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Variant: NM_194248.3(OTOF):c.2122C>T (p.Arg708Ter)

Version: 1.0

CA342562

21831 (ClinVar)

Gene: OTOF (HGNC:9381)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4e2e2716-c382-4845-b5ef-f5ff08cf37c4
Approved on: 2021/3/23
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HGVS expressions

NM_194248.3:c.2122C>T
NM_194248.3(OTOF):c.2122C>T (p.Arg708Ter)
NC_000002.12:g.26479356G>A
CM000664.2:g.26479356G>A
NC_000002.11:g.26702224G>A
CM000664.1:g.26702224G>A
NC_000002.10:g.26555728G>A
NG_009937.1:g.84343C>T
ENST00000272371.7:c.2122C>T
ENST00000272371.6:c.2122C>T
ENST00000403946.7:c.2122C>T
NM_001287489.1:c.2122C>T
NM_194248.2:c.2122C>T
NM_001287489.2:c.2122C>T

Pathogenic

Met criteria codes 4

PVS1 PP1_Strong PM3_Strong PP4

Not Met criteria codes 1

PM2

Evidence Links 0

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.2122C>T (p.Arg708Ter) variant in OTOF has been reported in reported in at least 11 individuals with autosomal recessive nonsyndromic hearing loss, including 2 probands who were compound heterozygous for a second nonsense variant in OTOF (confirmed in trans in one of these cases) and 9 homozygous probands, and segregated with disease in at least 17 affected family members from 7 families (PM3_Strong, PP1_Strong; PMID: 14635104, 18381613, 26029705, 29434063, 19250381; Partners Laboratory for Molecular Medicine unpublished data, ClinVar SCV000065176.6). It has also been identified in 0.0162% (4/24,692) of African/African-American alleles in gnomAD v2 (gnomad.broadinstitute.org). The p.Arg708Ter variant in OTOF is predicted to cause a premature stop codon in biologically-

relevant-exon 18/46 (NM_001287489) that leads to a truncated or absent protein in a gene in which loss-of-function is an established mechanism (PVS1; PMID: 30192042). At least one patient with this variant displayed features of auditory neuropathy spectrum disorder, which is highly specific for OTOF (PP4; Partners Laboratory for Molecular Medicine unpublished data, ClinVar SCV000065176.6). In summary, the p.Arg708Ter variant in OTOF meets criteria to be classified as pathogenic for autosomal recessive nonsyndromic hearing loss based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PVS1, PM3_Strong, PP1_Strong, PP4.

Met criteria codes

PVS1	✔	Occurs in exon 18/46 (NM_001287489).
PP1_Strong	✔	Segregated with disease in one large, consanguineous family with a published LOD score of 4.03 (PMID: 29434063) as well as 7 other families (PMID: 29434063, 26029705, 19250381, 14635104)
PM3_Strong	✔	Observed in the compound heterozygous state with a second nonsense variant in 2 cases; for one of these, the variants were confirmed as trans (1.5 PM3 points; PMIDs: 14635104, 18381613) and in the homozygous state in 9 other probands (max score for homozygous occurrences: 1 point; PMID: 29434063, 26029705, 19250381; Partners Laboratory for Molecular Medicine internal data, ClinVar SCV000065176.6).
PP4	✔	Observed in at least 1 proband with auditory dyssyncrhony (Partners Laboratory for Molecular Medicine internal data; ClinVar SCV000065176.6).

Not Met criteria codes

PM2	✖	Present in 0.0162% (4/24692) of African/African-American alleles in gnomAD v2. Present in 0.01447% (6/41454) of African/African-American alleles in gnomAD v3.

Curation History

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