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Variant: NM_194248.3(OTOF):c.2485C>T (p.Gln829Ter)

Version: 1.0

CA340525

6137 (ClinVar)

Gene: OTOF (HGNC:9381)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: fd96b31f-e928-4d10-85de-65170a3b6d72
Approved on: 2022/5/13
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HGVS expressions

NM_194248.3:c.2485C>T
NM_194248.3(OTOF):c.2485C>T (p.Gln829Ter)
NC_000002.12:g.26477210G>A
CM000664.2:g.26477210G>A
NC_000002.11:g.26700078G>A
CM000664.1:g.26700078G>A
NC_000002.10:g.26553582G>A
NG_009937.1:g.86489C>T
ENST00000272371.7:c.2485C>T
ENST00000339598.8:c.244C>T
ENST00000402415.8:c.244C>T
ENST00000272371.6:c.2485C>T
ENST00000338581.10:c.244C>T
ENST00000339598.7:c.244C>T
ENST00000402415.7:c.415C>T
ENST00000403946.7:c.2485C>T
NM_001287489.1:c.2485C>T
NM_004802.3:c.244C>T
NM_194248.2:c.2485C>T
NM_194322.2:c.415C>T
NM_194323.2:c.244C>T
NM_001287489.2:c.2485C>T
NM_004802.4:c.244C>T
NM_194322.3:c.415C>T
NM_194323.3:c.244C>T

Pathogenic

Met criteria codes 4

PP4 PVS1 PM3_Very Strong PP1_Strong

Not Met criteria codes 1

BS1

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 filtering allele frequency (the lower threshold of the 95% CI of 22/34228) of the c.2485C>T (p.Gln829Ter) variant in the OTOF gene is 0.04% for Latino chromosomes in gnomAD v2.1.1, which meets the cutoff to apply BS1_Supporting. However, this variant has been established as a founder variant in the Spanish population and is thought to be causative in 3% of cases of deafness in the Spanish population (BS1_Supporting not applicable; PMID: 27177047). The p.Gln829Ter variant in OTOF is predicted to cause a premature stop codon in biologically-relevant-exon 21/46 (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). The p.Gln829Ter variant has been identified in >50 patients with non-syndromic hearing loss (PM3_VeryStrong; PMIDs: 18381613, 17036997, 16371502, 14635104, 12114484). It has repeatedly been reported to segregate with hearing loss (PP1_Strong; PMIDs: 12114484, 14635104,16371502, 18381613). In addition to hearing loss, at least 24 patients reported to have the p.Gln829Ter variant presented with features of auditory neuropathy spectrum disorder, which is highly specific to OTOF and autosomal recessive hearing loss (PP4; PMIDs:18381613, 17036997, 14635104). In summary, the p.Gln829Ter 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, PP1_Strong, PM3_VeryStrong, PP4.

Met criteria codes

PP4	✔	auditory neuropathy observed in at least 12 patients (PMIDs: 14635104, 17036997)
PVS1	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3_Very Strong	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1_Strong	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Not Met criteria codes

BS1	✖	0.04% (22/34228 CI 95%) Latino alleles in gnomAD v2.1.1, all exomes 0.016% (2/2092 CI 95%) “Other” alleles and 0.005% (3/15278 CI 95%) Latino/Admixed American alleles in gnomAD v3.1

Curation History

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