The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_194248.2(OTOF):c.5098G>C

Version: 2.1

CA345132

48253 (ClinVar)

Gene: OTOF (HGNC:9381)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: a3a44624-d639-4324-a887-81890dc4927c
Approved on: 2024/6/28
Published on: 2024/6/28

HGVS expressions

NM_194248.2(OTOF):c.5098G>C
NC_000002.12:g.26463969C>G
CM000664.2:g.26463969C>G
NC_000002.11:g.26686837C>G
CM000664.1:g.26686837C>G
NC_000002.10:g.26540341C>G
NG_009937.1:g.99730G>C
ENST00000272371.7:c.5098G>C
ENST00000339598.8:c.2797G>C
ENST00000402415.8:c.2857G>C
ENST00000272371.6:c.5098G>C
ENST00000338581.10:c.2797G>C
ENST00000339598.7:c.2797G>C
ENST00000402415.7:c.3028G>C
ENST00000403946.7:c.5098G>C
ENST00000464574.1:n.847G>C
NM_001287489.1:c.5098G>C
NM_004802.3:c.2797G>C
NM_194248.2:c.5098G>C
NM_194322.2:c.3028G>C
NM_194323.2:c.2797G>C
NM_001287489.2:c.5098G>C
NM_004802.4:c.2797G>C
NM_194248.3:c.5098G>C
NM_194322.3:c.3028G>C
NM_194323.3:c.2797G>C

Pathogenic

Met criteria codes 4

PP3 PP4 PM3_Very Strong PP1_Strong

Not Met criteria codes 1

BS1

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*

PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.5098G>C (p.Glu1700Gln) variant in OTOF is a missense variant predicted to cause a substitution of glutamic acid by glutamine at amino acid 1700. The filtering allele frequency (the lower threshold of the 95% CI of 152/44874) of the c.5098G>C (p.Glu1700Gln) is 0.2948% for East Asian chromosomes by gnomAD v4.1.0, which meets the ClinGen Hearing Loss VCEP threshold (≥0.003) for BS1. However, based on the evidence outlined below, the ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for nonsyndromic hearing loss outweighs its high allele frequency the East Asian population, given it is reported as a founder mutation in the Taiwanese population (PMID: 20224275). Therefore, the BS1 code will not contribute to the overall classification. The computational predictor REVEL gives a score of 0.85 which is above the threshold of ≥ 0.7 (PP3). This variant has been detected in at least 18 individuals with autosomal recessive nonsyndromic hearing loss. Eight individuals were homozygous for the variant (PMIDs: 20224275, 35106950). Six individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (p.Glu841Lys, c.4961-1G>A, p.Arg1344*, p.Arg500*; PMID: 28766844). Four individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and confirmed in trans by parental testing (p.Pro1628Thr; PMID: 34692690) (PM3_VeryStrong). At least one patient with this variant displayed features of auditory neuropathy spectrum disorder, which is highly specific for OTOF (PP4; PMID: 28766844). The variant has been reported to segregate with hearing loss in multiple affected family members from two families (PP1_Strong; PMIDs: 20224275, 34692690). In summary, this variant meets the criteria to be classified as pathogenic for nonsyndromic genetic hearing loss, based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP (PP3, PM3_VeryStrong, PP4, PP1_Strong; Version 2; 5/15/24).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.85 which is above the threshold of ≥ 0.7 (PP3).
PP4	✔	At least one patient with this variant displayed features of auditory neuropathy spectrum disorder, which is highly specific for OTOF (PP4; PMID: 28766844).
PM3_Very Strong	✔	This variant has been detected in at least 18 individuals with autosomal recessive nonsyndromic hearing loss. Eight individuals were homozygous for the variant (PMIDs: 20224275, 35106950). Six individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant with phase unknown (p.Glu841Lys, c.4961-1G>A, p.Arg1344*, p.Arg500*; PMID: 28766844). Four individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and confirmed in trans by parental testing (p.Pro1628Thr; PMID: 34692690) (PM3_VeryStrong).
PP1_Strong	✔	The variant has been reported to segregate with hearing loss in multiple affected family members from two families (PP1_Strong; PMIDs: 20224275, 34692690).

Not Met criteria codes

BS1	✖	The filtering allele frequency (the lower threshold of the 95% CI of 152/44874) of the c.5098G>C (p.Glu1700Gln) is 0.2948% for East Asian chromosomes by gnomAD v4.1.0, which meets the ClinGen Hearing Loss VCEP threshold (≥0.003) for BS1. However, based on the evidence outlined below, the ClinGen Hearing Loss Expert Panel believes

that the evidence for the pathogenicity of this variant for nonsyndromic hearing loss outweighs its high allele frequency the East Asian population, given it is reported as a founder mutation in the Taiwanese population (PMID: 20224275). Therefore, the BS1 code will not contribute to the overall classification.

Curation History

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