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_194248.3(OTOF):c.5374C>T (p.Arg1792Cys)

Version: 1.2

CA182451

178503 (ClinVar)

Gene: OTOF (HGNC:9381)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 71c2ce3c-1d30-4ad1-b66d-cee7e0ffa15c
Approved on: 2023/6/29
Published on: 2023/6/30

HGVS expressions

NM_194248.3(OTOF):c.5374C>T (p.Arg1792Cys)
NM_194248.3:c.5374C>T
NC_000002.12:g.26461855G>A
CM000664.2:g.26461855G>A
NC_000002.11:g.26684723G>A
CM000664.1:g.26684723G>A
NC_000002.10:g.26538227G>A
NG_009937.1:g.101844C>T
ENST00000272371.7:c.5374C>T
ENST00000339598.8:c.3073C>T
ENST00000402415.8:c.3133C>T
ENST00000272371.6:c.5374C>T
ENST00000338581.10:c.3073C>T
ENST00000339598.7:c.3073C>T
ENST00000402415.7:c.3304C>T
ENST00000403946.7:c.5374C>T
NM_001287489.1:c.5374C>T
NM_004802.3:c.3073C>T
NM_194248.2:c.5374C>T
NM_194322.2:c.3304C>T
NM_194323.2:c.3073C>T
NM_001287489.2:c.5374C>T
NM_004802.4:c.3073C>T
NM_194322.3:c.3304C>T
NM_194323.3:c.3073C>T

Likely Pathogenic

Met criteria codes 5

PM3 PM5 PM2_Supporting PP3 PP4

Not Met criteria codes 18

PM1 PM4 PM6 BA1 BS2 BS1 BS4 BP4 BP3 BP2 BP5 BP7 PS1 PS2 PS3 PS4 PVS1 PP1

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

Evidence Links 0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.5374C>T variant in OTOF is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 1792. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006152 (1/16256 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 0.843, which is above the threshold of 0.7, evidence that correlates with impact to OTOF function (PP3). 1 different missense variant, c.5375G>A (p.R1792H) (PMID: 29048421, ClinVar Variation ID: 48259), in the same codon has been classified as likely pathogenic for nonsyndromic hearing loss by multiple submitters in ClinVar (PM5). This variant has been detected in at least 3 individuals with AR deafness. For two of those individuals, both were compound heterozygous for the variant and a VUS meeting PM2_Supporting, and both of those were confirmed in trans by family testing (c.2676G>A (p.K892K) which occurs at the last nucleotide in exon (22) of OTOF and c.4748G>A (p.R1583H), 1.5 PM3 points, PMID: 34416374, Universitätsmedizin Göttingen, Institute of Human Genetics/Institute of Auditory Neuroscience & InnerEarLab) (PM3). At least one patient was compound heterozygous for this variant and the p.K892K variant displayed auditory neuropathy spectrum disorder (ANSD), which is highly specific for autosomal recessive deafness (PP4, PMID: 34416374). 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, PP4, PM3, PM5 (ClinGen Hearing Loss VCEP specifications version 2; 6/27/2022).

Met criteria codes

PM3	✓	This variant has been detected in at least 3 individuals with AR deafness. For two of those individuals, both were compound heterozygous for the variant and a VUS meeting PM2_Supporting, and both of those were confirmed in trans by family testing (c.2676G>A (p.K892K) which occurs at the last nucleotide in exon (22) of OTOF and c.4748G>A (p.R1583H), 1.5 PM3 points, PMID: 34416374, Universitätsmedizin Göttingen, Institute of Human Genetics/Institute of Auditory Neuroscience & InnerEarLab) (PM3).
PM5	✓	1 different missense variant, c.5375G>A (p.R1792H) (PMID: 29048421, ClinVar Variation ID: 48259), in the same codon has been classified as likely pathogenic for nonsyndromic hearing loss by multiple submitters in ClinVar (PM5).
PM2_Supporting	✓	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006152 (1/16256 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).
PP3	✓	The computational predictor REVEL gives a score of 0.843, 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 the p.K892K variant displayed auditory neuropathy spectrum disorder (ANSD), which is highly specific for autosomal recessive deafness (PP4, PMID: 34416374).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 3 of 3 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.