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_004004.5(GJB2):c.101T>C (p.Met34Thr)

Version: 1.0

CA172206

17000 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: e8b1ce82-bc97-4baf-b442-294c2a6849cd
Approved on: 2019-06-24
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HGVS expressions

NM_004004.5:c.101T>C
NM_004004.5(GJB2):c.101T>C (p.Met34Thr)
NC_000013.11:g.20189481A>G
CM000675.2:g.20189481A>G
NC_000013.10:g.20763620A>G
CM000675.1:g.20763620A>G
NC_000013.9:g.19661620A>G
NG_008358.1:g.8495T>C
NM_004004.6:c.101T>C
ENST00000382844.1:c.101T>C
ENST00000382848.4:c.101T>C

Pathogenic

Met criteria codes 4

PS4 PP1 PP3 PM3_Very Strong

Not Met criteria codes 19

PVS1 BS2 BS1 BS4 BP5
BP7 BP4 BP3 BP2 PM6
PM2 PS1 PS2 PS3 PM1
PM5 PM4 PP4 BA1

Evidence Links 9

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 510/25108) of the c.101T>C (p.Met34Thr) variant in the GJB2 gene is 1.46% for European (non-Finnish) genomes in gnomAD. This is a high enough frequency that, in the absence of conflicting data, might warrant a benign classification based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss variants (BA1). 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 in population databases. Therefore, the BA1 code will not contribute to the overall classification. The homozygous genotype and compound heterozygous genotype with another variant in GJB2 have shown to be statistically enriched in patients with nonsyndromic sensorineural hearing loss compared to individuals

representative of the general population in gnomAD and/or those who underwent carrier screening at Counsyl. (PS4; PMID: 31160754). This study also reported the variant in 27 homozygous affected probands, 17 affected probands with the p.Val37Ile variant in trans, 138 affected probands with a variant asserted to be P/LP in ClinVar, and 78 affected probands with a premature GJB2 termination codon in trans (PM3; PMID 31160754). The REVEL computational prediction analysis tool produced a score of 0.702, which is above the threshold necessary to apply PP3. Most dye transfer and electrical coupling assays support that the variant impacts protein function (PMID: 16849369, 12189493, 10556284, 16300957, 15033936, 12189493); however, some assays showed partial function (PMID: 27884957), and therefore this evidence was not counted. At least 16 segregations of the p.Met34Thr variant in family members have been described (PP1_Strong, PMID: 31160754, 10903123). Of note, the severity of hearing loss is known to be mild on average and there have been multiple accounts of incomplete penetrance of the variant in families/individuals with p.Met34Thr in a biallelic genotype. In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive nonsyndromic genetic hearing lossbased on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PS4, PP1_Strong, PM3, PP3.

Met criteria codes

PS4	✔	The homozygous genotype and compound het genotype with another path variant in GJB2 has been shown to be statistically enriched in patients with nonsydromic sensorineural hearing loss compared to individuals representative of the general population from carrier screening from Counsyl and/or gnomAD data. See Table 2 from this publication This study collected data from 15 different clinical sequencing sites and identified a total of 391 probands with the M34T allele out of 17,635 affected probands screened for GJB2. Additionally they found that 29/17,635 affected probands were homozygous for the M34T relative to 81/802,339 homozygous M34T individuals from the general population. This indicates that the homozygous genotype was significantly increased in the affected population. This was replicated in the European subpopulations, and it was also found that there were a highly significant amount of compound heterozygous individuals in the European affected subpopulation relative to that of Counsyl's carrier screening cohort. Both p values were <0.0001. PubMed:31160754
PP1	✔	This paper described 16 segregations of the p.Met34Thr variant in homozygous/compound het occurrences in Supplementary table S2 This paper identifies 6 families in which the M34T variant didn't segregate with hearing loss "The M34T mutation did not segregate with the deafness in six of the seven familial forms of NSSNH. Eight persons with normal audiogram presented a heterozygous M34T variation and five normal hearing individuals were composite heterozygous for M34T and another GJB2 mutation. Four normal hearing individuals with a documented audiogram were M34T/35delG and one was M34T/(GJB6D13S1830)del" HOWEVER, none of these patients were genotype positive phenotype negative. These could all be explained by the fact that this is a common variant and it may just be a carrier variant with a different cause in the probands. They did identify one homozygous segregation family N'7. PubMed:14694360 Patient I:2, the mother of 2 chilldren homozygous for the 167delT variant in GJB2 was compound heterozygous for the M34T variant and the 167delT variant and did not possess the phenotype. This may be due to a lack of penetrance and therefore BS4 shouldn't be applied. PubMed:10903123 This paper described 16 segregations of the p.Met34Thr variant in homozygous/compound het occurrences in Supplementary table S2 PubMed:31160754
PP3	✔	REVEL score of the variant is 0.702 which is above the HL VCEP's threshold for PP3
PM3_Very Strong	✔	This study showed that the p.Met34Thr variant occurred in 27 homozygous probands, 17 times in trans with the p.Val37Ile variant, 138 times in trans with a P/LP variant and 78 times in trans with a premature termination codon in GJB2. This more than maxes out the PM3_VS points. PMID 31160754

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Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	There have been at least 2 confirmed accounts of incomplete penetrance of the M34T variant. In two Ashkenazi Jewish compound heterozygotes, the M34T variant was seen in trans with the p.Leu90Pro in one case and the p.Leu56Argfs varint in another case. Both individuals were confirmed to be unaffected by audiological evaluation. However, the homozygous genotype has been shown to be statistically enriched in patients with hearing loss relative to those in the general population. Therefore this code cannot be applied. This study described two confirmed accounts of incomplete pentrance of the M34T variant. In two Ashkenazi Jewish compound heterozygotes, the M34T variant was seen in trans with the p.Leu90Pro in one case and the p.Leu56Argfs varint in another case. Both individuals were confirmed to be unaffected by audiological evaluation. PubMed:31160754
BS1	✖	see BA1 Showed this variant is statistically enriched in affected populations therefore BA1 should not be applied PubMed:31160754
BS4	✖	Decreased penetrance is expected of this variant so BS4 wouldn't apply This paper identifies 6 families in which the M34T variant didn't segregate with hearing loss "The M34T mutation did not segregate with the deafness in six of the seven familial forms of NSSNH. Eight persons with normal audiogram presented a heterozygous M34T variation and five normal hearing individuals were composite heterozygous for M34T and another GJB2 mutation. Four normal hearing individuals with a documented audiogram were M34T/35delG and one was M34T/(GJB6D13S1830)del" HOWEVER, none of these patients were genotype positive phenotype negative. These could all be explained by the fact that this is a common variant and it may just be a carrier variant with a different cause in the probands. They did identify one homozygous segregation family N'7. PubMed:14694360 Patient I:2, the mother of 2 chilldren homozygous for the 167delT variant in GJB2 was compound heterozygous for the M34T variant and the 167delT variant and did not possess the phenotype. This may be due to a lack of penetrance and therefore BS4 shouldn't be applied. PubMed:10903123 This paper described 16 segregations of the p.Met34Thr variant in homozygous/compound het occurrences in Supplementary table S2 PubMed:31160754
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

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	✖	This study showed that the p.Met34Thr variant occurred in 27 homozygous probands, 17 times in trans with the p.Val37Ile variant, 138 times in trans with a P/LP variant and 78 times in trans with a premature termination codon in GJB2. This more than maxes out the PM3_VS points. PubMed:31160754
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	See BA1 Showed this variant is statistically enriched in affected populations therefore BA1 should not be applied PubMed:31160754
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	✖	Several studies have shown that the p.M34T variant has an impact on the formation and function of the Cx26 channel via dye transfer assays and electrical coupling assays. There were no mouse/ animal models found via lit search. It has also been suggested that this variant may have a dominant negative impact functionally as well though this hasn't really been supported in human cases. PMIDs: 16849369, 12189493, 10556284, 16300957, 15033936, 12189493. This criteria was not counted however because in de Wolf et al. 2016 there was residual function of the p.M34T Cx26 protein, therefore we decided to be conservative and not score this criterion. This study also showed that dye transfer and electrical coupling was impacted by the M34T variant. In addition, they showed that oligomerization of the variant Cx26 was reduced. PubMed:10556284 Dominant negative studies in oocytes showed that the M34T variant impacted the conductance of the oocytes but not the localization. PubMed:15033936 However, c.101T>C transfected HeLa cells were able to load the dye in response to nonphysiological zero extracellular Ca2+ stimulus, suggesting that p.Met34Thr variant connexin hemichannels may retain some residual function under unusual circumstances. PubMed:27884957 This study did both dye transfer assays and electrical coupling assays and showed that the M34T variant was defective with respect to wild type as well as the p.Arg127His variant which has been classified as Benign/LB by several labs in ClinVar. This served as a negative control as it did not impact the ability to form channels. PubMed:16849369 Tracer coupling experiments showed impacted dye coupling, reduced oligomerization relative to the WT. PubMed:12189493 This study showed that p.M34T, p.V37I and p.I82M, but NOT 4 other variants in GJB2 exerted a dominant inhibitory effect via Western blot in Xenopus oocytes. This study shoulnd't be used for this recessive curation. PubMed:16300957

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	The M34T variant is the more established pathogenic variant, therefore, despite the fact that c.101T>G (p.Met34Arg) has been classified as LP by the LMM, that variant would be the one that would be awarded PM5.
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	GJB2 has not been designated by the HL VCEP to be a gene who's variants can be awarded PP4
BA1	✖	This variant was detected in 510/25108 European (Finnish) alleles in gnomAD. The calculated filtering allele frequency in European (non-Finnish) genomes is 0.01462 (1655/128490) with 18 homozygotes. There are 28 homozygotes in gnomAD. However, this variant is statistically enriched in affected populations as shown by Shen et al. 2019 and therefore BA1 should not be applied. Showed this variant is statistically enriched in affected populations therefore BA1 should not be applied PubMed:31160754

Curation History

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