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Variant: m.12201T>C

Version: 1.1

CA259740

30004 (ClinVar)

Gene: MT-TH (HGNC:4564)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 6c102897-0080-4a7d-a221-5b0063f8108a
Approved on: 2023/4/17
Published on: 2023/5/19

HGVS expressions

NC_012920.1:m.12201T>C
J01415.2:m.12201T>C

Likely Pathogenic

Met criteria codes 5

PP3 PS3_Moderate PM2_Supporting PS4_Supporting PP1_Moderate

Not Met criteria codes 2

PM6 PS2

Evidence Links 0

Expert Panel

Mitochondrial Diseases VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The m.12201T>C variant in MT-TH has been reported in three families with features of primary mitochondrial disease (PS4_supporting). The first family reported was 5-generation Han Chinese family with late-onset non-syndromic deafness (PMIDs: 21931169, 24920829, 31819004, 32169613). A second case was reported in a Vietnamese cohort of children with non-syndromic hearing loss (https://www.ojhas.org/issue65/2018-1-6.html). The third case was reported in a cohort of individuals with dilated cardiomyopathy (PMID: 34991096). Seventeen of 35 matrilineal relatives in the first reported family exhibited variable severity and age at onset of sensorineural hearing loss and blood heteroplasmy levels correlated with both onset age and symptom severity (PP1_moderate). There are no reported de novo occurrences of this variant to our knowledge. Although there are several occurrences in population databases, the frequency is still low (PM2_supporting). The computational predictor MitoTIP suggests this variant is pathogenic (67th percentile) and HmtVAR predicts it to be pathogenic score of 0.5 (PP3). Cybrid studies show different classes of function defects including a decrease in the steady-state level of tRNAHis, diminished respiratory capacity, marked decreases in mtATP levels and membrane potential, increased reactive oxygen

species (ROS) production, decreased melting temperature, conformational changes, and instability of the mutated tRNA, and HARS2 overexpression corrected the mitochondrial dysfunction (PS3_moderate; PMIDs: 24920829, 31819004). In summary, this variant meets criteria to be classified as likely pathogenic for primary mitochondrial disease inherited in a mitochondrial manner. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on April 17, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_supporting, PP1_moderate, PM2_supporting, PP3, PS3_moderate.

Met criteria codes

PP3	✔	The computational predictors MitoTIP and HmtVar calculated that this variant would cause a negative functional impact, with pathogenic scores of 0.67 and 0.50 respectively. (PP3)
PS3_Moderate	✔	Two functional studies reported an extensive array of detrimental effects of this variant. Mutant cybrids (PMID 24920829) showed ~70% decrease in the steady-state level of tRNAHis, diminished respiratory capacity, marked decreases in mtATP levels and membrane potential, and increased ROS production. A later paper by the same group (PMID 31819004) demonstrated that m.12201T>C perturbs the tRNAHis structure and function with decreased melting temperature, conformational changes, and instability of the mutated tRNA. Resultant alteration of aminoacylation tRNAHis caused mitochondrial translational defects and respiratory deficiency. Transfer of HARS2 into the mutant cybrids raised the levels of aminoacylated tRNAHis from 56.3 to 75.0% but did not change the aminoacylation of other tRNAs. The addition of HARS2 greatly improved tRNA metabolism, the efficiency of mitochondrial translation, activities of oxidative phosphorylation complexes, and respiration capacity. HARS2 over-expression markedly increased mitochondrial ATP levels and membrane potential and reduced the production of ROS in mutant cells. These results indicate that HARS2 over-expression corrects the mitochondrial dysfunction caused by m.12201T>C.
PM2_Supporting	✔	The m.12201T>C variant is present in Mitomap's GenBank dataset at less than 1/50,000 or 0.002% (1/59,389 sequences, 0.00168%, haplogroup R23). It is absent in the gnomAD3.1.2 (0/56433 sequences) and absent in homoplasmic form in Helix (0/195,583 sequences) databases Three heteroplasmic occurrences were reported in Helix (3/195,583, .00153%, haplogroups H, T, W). Databases were last queried on 4/13/2023.
PS4_Supporting	✔	The m.12201T>C variant in MT-TH has been reported in one very large Han Chinese family with late-onset non-syndromic deafness (PMID 21931169, 24920829, 31819004, 32169613). The average age at onset of hearing loss in the large Chinese pedigree was 29 years. Seventeen of 35 matrilineal relatives in this family exhibited variable severity and age at onset of sensorineural hearing loss; blood heteroplasmy levels correlated with both onset age and symptom severity. Heteroplasmy was determined by pyrosequencing. A second case was reported in a Vietnamese cohort of 76 families with non-syndromic hearing loss (https://www.ojhas.org/issue65/2018-1-6.html). Another case was found in a cohort of dilated cardiomyopathy patients (PMID 34991096). Additionally, A MELAS patient was reported by the Baylor lab (PMIDs 31965079, 23463613; ClinVar 30004) but this report was not tallied as part of the case count.
PP1_Moderate	✔	Seventeen of 35 matrilineal relatives in a Chinese Han family exhibited variable severity and age at onset of sensorineural hearing loss; blood heteroplasmy levels correlated with both onset age and symptom severity. Heteroplasmy was determined by Sanger/BigDye Sequencing.

Not Met criteria codes

PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.12201T>C	Likely Pathogenic	Mitochondrial Disease	2023-05-19	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-TH
View	m.12201T>C	Likely Pathogenic	Mitochondrial Disease	2023-05-19	1.0	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	N/A

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