Variant: m.7511T>C

Version: 1.1

CA340922

9566 (ClinVar)

Gene: MT-TS1 (HGNC:4574)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: f6e90622-5af5-426c-8f67-770c91a0c91b
Approved on: 2022-11-30
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HGVS expressions

NC_012920.1:m.7511T>C
J01415.2:m.7511T>C

Likely Pathogenic

Met criteria codes 3

PP3 **PS3_Moderate** **PS4_Moderate**

Not Met criteria codes 3

PP1 **PM6** **PM2**

Evidence Links 2

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.7511T>C variant in MT-TS1 has been reported in ten unrelated probands from ten kindreds of varying ethnic background with nonsyndromic sensorineural hearing loss (PS4_moderate; PMIDs: 10371545, 12461693, 15670746, 18340555, 26279247, 25968158, 28320335, 29257206). In these families, the variant is present in family members with and without hearing loss. Hearing loss was variable overall when present, ranging from mild to profound. Age of onset of hearing loss varied from childhood to adulthood. Hearing loss was stable in some individuals and progressive in others. Some individuals also reported tinnitus and vertigo. There has been no other organ system involvement reported to date (although it is not clear if other organ systems were assessed in affected individuals). Muscle biopsy was not routinely performed in affected individuals however one individual did have COX-deficient fibers and complex IV deficiency (PMID: 10371545). The variant was generally present at homoplasmy (in maternal family members with and without hearing loss), however there were some heteroplasmic occurrences (PMIDs: 10371545, 12461693, 15670746, 26279247, 29257206). Penetrance differed across reported families, and several modifying factors were discussed, including variants in the genes PCDH15 (PMID: 26279247) and YARS2

(PMID: 25968158). Affected and unaffected individuals in these families had the variant and there was no correlation between severity and heteroplasmy level, thus preventing consideration for PP1. There are no de novo occurrences of this variant reported to our knowledge. The computational predictor MitoTIP suggests this variant is pathogenic (78.1 percentile) and HmtVAR predicts it to be pathogenic score of 0.75 (PP3). This variant is present in the healthy population, which is to be expected given the known reduced penetrance of this variant. Single fiber testing (PMID: 10371545) and cybrid analysis (PMID: 14960712) support the pathogenicity of this variant (PS3_moderate), as do other functional assays performed (PMIDs: 31685661, 16361254). This variant meets criteria to be classified as of uncertain significance however this Expert Panel elected to modify the classification to likely pathogenic given the overwhelming evidence of pathogenicity. Furthermore, the mitochondrial DNA variant specifications are known to not be optimized for variants that tend to be homoplasmic in nature and/or have reduced penetrance, such as the common mitochondrial variants associated with nonsyndromic hearing loss. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on November 30, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_moderate, PS3_moderate, PP3.

Met criteria codes

PP3	ℹ	✓	The computational predictor MitoTIP suggests this variant is pathogenic (78.1 percentile) and HmtVAR predicts it to be pathogenic score of 0.75 (PP3).
PS3_Moderate		✓	Single fiber testing (PMID: 10371545) and cybrid analysis (PMID: 14960712) support the pathogenicity of this variant (PS3_moderate), as do other functional assays performed (PMIDs: 31685661, 16361254). Single fiber testing supports pathogenicity. **PubMed:10371545** Cybrid analysis supports pathogenicity. **PubMed:14960712**
PS4_Moderate	ℹ	✓	The m.7511T>C variant in MT-TS1 has been reported in ten unrelated probands from ten kindreds of varying ethnic background with nonsyndromic sensorineural hearing loss (PS4_moderate; PMIDs: 10371545, 12461693, 15670746, 18340555, 26279247, 25968158, 28320335, 29257206). In these families, the variant is present in family members with and without hearing loss. Hearing loss was variable overall when present, ranging from mild to profound. Age of onset of hearing loss varied from childhood to adulthood. Hearing loss was stable in some individuals and progressive in others. Some individuals also reported tinnitus and vertigo. There has been no other organ system involvement reported to date (although it is not clear if other organ systems were assessed in affected individuals). Muscle biopsy was not routinely performed in affected individuals however one individual did have COX-deficient fibers and complex IV deficiency (PMID: 10371545). The variant was generally present at homoplasmy (in maternal family members with and without hearing loss), however there were some heteroplasmic occurrences (PMIDs: 10371545, 12461693, 15670746, 26279247, 29257206). Penetrance differed across reported families, and several modifying factors were discussed, including variants in the genes PCDH15 (PMID: 26279247) and YARS2 (PMID: 25968158).

Not Met criteria codes

PP1	ℹ	✗	Affected and unaffected individuals in these families had the variant and there was no correlation between severity and heteroplasmy level, thus preventing consideration for PP1.
PM6	ℹ	✗	There are no de novo occurrences of this variant reported to our knowledge.
PM2		✗	This variant is present in the healthy population, which is to be expected given the known reduced penetrance of this variant.

Curation History

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