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Variant: m.15990C>T

Version: 1.1

CA120549

9570 (ClinVar)

Gene: MT-TP (HGNC:4571)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: b912a68d-9994-41de-aec5-ef178e90013b
Approved on: 2023/2/13
Published on: 2023/4/3

HGVS expressions

NC_012920.1:m.15990C>T
J01415.2:m.15990C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM6 PS3_Supporting PS4_Supporting

Not Met criteria codes 2

PP1 PP3

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.15990C>T variant in MT-TP gene has been reported in two unrelated individuals with primary mitochondrial disease (PS4_supporting). The age of onset ranged from the first decade of life to adulthood. Features seen in these individuals include chronic progressive external ophthalmoplegia (CPEO), myopathy, and exercise intolerance (PMIDs: 32305257, 7689388, 8190311). The variant occurred de novo in both individuals (PM6; PMIDs: 7689388, 8190311, 32305257). There are no other large families reported in the medical literature to consider for evidence of segregation. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). In silico predictors are conflicting as the computational predictor MitoTIP suggests this variant is pathogenic (51.7 percentile) but HmtVAR predicts it to be neutral with a score of 0.1. Single fiber testing in both reported individuals support the functional impact of this variant (PS3_supporting). In one study, there were higher levels of the variant in COX-negative fibers (91-97%) than in COX-positive fibers (63-86%, p= < 0.001; PMID: 7689388). In the other study, there were again higher levels of the variant in COX-negative fibers (89.75 ± 6.84%, n = 20) than in COX-positive fibers (14.00 ± 6.84 %, n = 17; p < 0.001; PMID: 32305257). In summary, this variant

meets criteria to be classified as uncertain significance however, after extensive discussion, this Expert Panel elected to modify the classification to likely pathogenic given the consistent phenotype and functional testing performed in each reported individual. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on February 13, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_supporting, PM2_supporting, PM6, PS3_supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PM6	✔	The variant occurred de novo in both individuals (PM6; PMIDs: 7689388, 8190311, 32305257). -- This variant occurred de novo in 2 individuals, one case undetectable in mother & maternal sister in white blood cells and fibroblasts via restriction fragment length polymorphism (RFLP) analysis of PCR amplified fragments and in the other case could not be detected in DNA extracted from blood, urothelial cells, buccal cells and hair shafts in the mother (PM6_supporting, PMID: 7689388, 8190311, 32305257).
PS3_Supporting	✔	Single fiber testing in both reported individuals support the functional impact of this variant (PS3_supporting). In one study, there were higher levels of the variant in COX-negative fibers (91-97%) than in COX-positive fibers (63-86%, p= < 0.001; PMID: 7689388). In the other study, there were again higher levels of the variant in COX-negative fibers (89.75 ± 6.84%, n = 20) than in COX-positive fibers (14.00 ± 6.84 %, n = 17; p < 0.001; PMID: 32305257). statistically-significantly higher mutation load in COX-deficient fibers [89.75 ±6.84 (n = 20)] than in COX positive fibers [14.00 ±6.84 (n = 17)] (p < 0.001) PubMed:32305257 COX neg fibers mutant mtDNA 91-97% vs normal COX fibers 63-86% p <0.001 PubMed:7689388
PS4_Supporting	✔	The m.15990C>T variant in MT-TP gene has been reported in two unrelated individuals with primary mitochondrial disease (PS4_supporting). The age of onset ranged from the first decade of life to adulthood. Features seen in these individuals include chronic progressive external ophthalmoplegia (CPEO), myopathy, and exercise intolerance (PMIDs: 32305257, 7689388, 8190311).

Not Met criteria codes

PP1	✖	There are no large families reported in the medical literature to consider for evidence of segregation.
PP3	✖	In silico predictors are conflicting as the computational predictor MitoTIP suggests this variant is pathogenic (51.7 percentile) but HmtVAR predicts it to be neutral with a score of 0.1.

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.15990C>T	Likely Pathogenic	Mitochondrial Disease	2023-04-03	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-TP
View	m.15990C>T	Likely Pathogenic	Mitochondrial Disease	2023-04-03	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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