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Variant: NC_012920.1(MT-CYB):m.618T>C

Version: 1.1

CA913175634

689818 (ClinVar)

Gene: MT-TF (HGNC:4558)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 0d13b67a-3329-4a86-9afb-6fb8aa50aa94
Approved on: 2024/9/9
Published on: 2025/5/14

HGVS expressions

NC_012920.1:m.618T>C
J01415.2:m.618T>C

Uncertain Significance

Met criteria codes 3

PS3_Supporting PM2_Supporting PP3

Not Met criteria codes 3

PM6 PS4 PP1

Evidence Links 1

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.618T>C variant in MT-TF has been reported in one individual with primary mitochondrial disease (PMID: 9636664). This person had myopathy with ragged red fibers on muscle biopsy and reduced activities of electron transport chain enzyme complexes I and III in muscle. The variant was present at 95% heteroplasmy in skeletal muscle and 20% in blood. The variant was undetectable in blood from his healthy sister. There are no other families or de novo occurrences of this variant reported to our knowledge. There is one heteroplasmic occurrence of this variant in the Helix dataset and this variant is absent in the MITOMAP GenBank dataset and in gnomAD v3.1.2 (PM2_supporting). The computational predictor MitoTIP suggests this variant is pathogenic (65.8 percentile) and HmtVAR predicts it to be pathogenic score of 0.6 (PP3). No cybrid or single-fiber studies were performed. However, a significant loss in aminoacylation efficiency was demonstrated and, when a compensatory variant was introduced to restore Watson–Crick base pairing in the anti-codon stem, the double mutant fully restored aminoacylation (PS3_supporting; PMID: 17878308). In summary, this variant meets criteria to be classified as uncertain significance 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 September 9, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM2_supporting, PP3, PS3_supporting.

Met criteria codes

PS3_Supporting	✔	No cybrid or single-fiber studies were performed. However, a significant loss in aminoacylation efficiency was demonstrated and when a compensatory variant was introduced to restore Watson–Crick base pairing in the anti-codon stem, the double mutant fully restored aminoacylation (PS3_supporting; PMID: 17878308). This study by Ling et al 2007 (PMID 17878308) demonstrated a significant loss in aminoacylation efficiency with mutation m.618T>C. Additionally, they introduced a compensatory mutation to restore Watson–Crick base pairing in the anti-codon stem and found that the double mutant exhibited fully restored aminoacylation. PubMed:17878308
PM2_Supporting	✔	There is one heteroplasmic occurrence of this variant in the Helix dataset and this variant is absent in the MITOMAP GenBank dataset and in gnomAD v3.1.2 (PM2_supporting).
PP3	✔	In-silico scores were ranked in the “possibly pathogenic” range in both MitoTip, 0.658 (raw score 14.848) and HmtVar, 0.6.

Not Met criteria codes

PM6	✖	No assumed de novo cases were found in our review of the literature.
PS4	✖	The m.618T>C variant in MT-TF has been reported in one individual with primary mitochondrial disease (PMID: 9636664). This person had myopathy with ragged red fibers on muscle biopsy and reduced activities of electron transport chain enzyme complexes I and III in muscle. The variant was present at 95% heteroplasmy in skeletal muscle and 20% in blood.
PP1	✖	The variant was heteroplasmic in the patient's skeletal muscle (95% mutant) and peripheral blood cells (20% mutant) but was undetectable in blood cells from his healthy sister. No other case reports were found in our review of the literature.

Curation History

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