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# *Variant: m.7587T>C*

Version: 2.0

*CA120604*

*9658 (ClinVar)*

**Gene**: MT-CO2 (HGNC:4513)
**Condition**: mitochondrial disease (MONDO:0044970)
**Inheritance Mode**: Mitochondrial inheritance
**UUID:** 2338fdba-0964-469b-9310-a485936ee040
**Approved on**: 2024/3/11
**Published on**: 2024/11/19

## *HGVS expressions*

**NC_012920.1:m.7587T>C**
J01415.2:m.7587T>C
ENST00000361739.1:c.2T>C

**Likely Pathogenic**

**Met criteria codes** 4

PP3 PVS1_Strong PM2_Supporting PS3_Supporting

**Not Met criteria codes** 5

PP1 PP4 PM6 PS2 PS4

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.7587T>C (p.M1T) variant in MT-CO2 has been reported in one family with primary mitochondrial disease to date (PMID: 10205264). Affected individuals in this family include a 57-year-old woman with fatigue and unsteady gait and her more severely affected son who was nonambulatory and had cognitive impairment, optic atrophy, pigmentary retinopathy, and distal muscle wasting. The variant was present at 67% heteroplasmy in the muscle of the mother and at 91% in muscle of her affected son. There are no individuals reported with de novo occurrences of this variant to our knowledge. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.79 (Min=0, Max=1; APOGEE2 score is 0.875), which predicts a damaging effect on gene function (PP3). This initiation codon variant results in a significant truncation of the MT-CO2 protein (PVS1_strong). Single fiber testing showed higher levels of the variant in COX-negative (near homoplasmy) than in COX-positive fibers (17–52%; PS3_supporting, PMID: 10205264). 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 March 11, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PVS1_strong, PP3, PS3_supporting, PM2_supporting.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✔ | The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.79 (Min=0, Max=1; APOGEE2 score is 0.875), which predicts a damaging effect on gene function (PP3). |
| **PVS1_Strong** | ✔ | This initiation codon variant results in a significant truncation of the MT-CO2 protein (PVS1_strong). |
| **PM2_Supporting** | ✔ | This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). |
| **PS3_Supporting** | ✔ | A single fiber study of the patient's muscle showed clearly that the m.7587T>C variant segregated with a biochemical defect: the C allele was at much higher load in COX-negative fibers than in COX-positive fibers (PMID 10205264).<br><br>A single fiber study of the patient's muscle showed clearly that the m.7587T>C variant segregated with a biochemical defect: the C allele was at much higher load in COX-negative fibers than in COX-positive fibers PubMed:10205264 |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PP1** | ✖ | Only one segregation of m.7587T>C was observed in the family: the mildly affected mom had 67% heteroplasmy in muscle, while her severely affected son had 91% in muscle. The unaffected old son declined testing (PMID 10205264). |
| **PP4** | ✖ | The mutation was shown to cause a decrease in COX activity when the mutant load was >55%–65%. In fibroblasts from the affected son, which contained >95% mutated mtDNA, there was no detectable synthesis or any steady-state level of COX II. However, nuclear causes of isolated COX deficiency were not ruled out (PMID 10205264). |
| **PM6** | ✖ | There are no individuals reported with de novo occurrences of this variant to our knowledge. |
| **PS2** | ✖ | There are no individuals reported with de novo occurrences of this variant to our knowledge. |
| **PS4** | ✖ | The m.7587T>C variant in MT-CO2 has been reported in only one family to date, a 57-year-old woman with fatigue and unsteady gait with a severely affected, wheelchair-bound son. He was severely cognitively impaired with bilateral optic atrophy, pigmentary retinopathy, a marked decrease in color vision, and mild distal-muscle wasting. An older son was clinically unaffected at age 30 (PMID 10205264). |

Curation History

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| See Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | m.7587T>C | Likely Pathogenic | Mitochondrial Disease | 2024-11-19 | 2.0 | ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA | MT-CO2 |
| View | m.7587T>C | Likely Pathogenic | Mitochondrial Disease | 2024-11-19 | 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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