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Variant: m.5556G>A

Version: 1.1

CA128833

30007 (ClinVar)

Gene: MT-TW (HGNC:4578)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 3d3a75d1-4e33-42cf-8383-4d05613ffa96
Approved on: 2024/5/28
Published on: 2025/7/16

HGVS expressions

NC_012920.1:m.5556G>A
J01415.2:m.5556G>A

Likely Pathogenic

Met criteria codes 2

PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PS4 PP3

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.5556G>A variant in MT-TW has been reported in one individual with mitochondrial disease to date (PMID: 19809478). This was a girl with feeding difficulty and reflux onset shortly after birth and developmental regression beginning at age seven months. She also had constipation, failure to thrive, and died at 13 months due to respiratory insufficiency. She had metabolic acidosis and elevated blood and cerebrospinal fluid lactate. There was reduced activities of complexes I, III, and IV in skeletal muscle and fibroblasts, and reduced levels of fully assembled complexes I, III, IV, and V in fibroblast cell line. Mitochondrial protein synthesis and tRNA tryptophan levels were reduced in patient fibroblasts. The variant was present at 92% heteroplasmy in fibroblasts and 93% in skeletal muscle. The variant was not detectable in mother's blood, hair, urine, or skeletal muscle (PM6_supporting; PMID: 27450679). This variant is absent in the MITOMAP GenBank dataset, gnomAD v3.1.2, and the Helix dataset (PM2_supporting). In silico prediction tools are conflicting as the computational predictor MitoTIP suggests this variant is tolerated (44.5 percentile) but HmtVAR predicts it to be deleterious (score of 0.85). Cybrids with high heteroplasmy levels (90%, 93%, 96%) were generated and showed a pattern consistent with patient fibroblasts, and tRNA tryptophan

levels were reduced in cybrids to 33% (PS3_supporting; PMID: 19809478). In summary, this variant meets criteria to be classified as uncertain significance for primary mitochondrial disease however, after extensive discussion, this Expert Panel elected to modify the classification to likely pathogenic given the high heteroplasmy levels correlating with a severe phenotype with confirmed de novo status of the variant and compelling functional validation. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on May 28, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM6_supporting, PM2_supporting, PS3_supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the MITOMAP GenBank dataset, gnomAD v3.1.2, and the Helix dataset (PM2_supporting).
PS3_Supporting	✔	Cybrids with high heteroplasmy levels (90%, 93%, 96%) were generated and showed a pattern consistent with patient fibroblasts, and tRNA tryptophan levels were reduced in cybrids to 33% (PS3_supporting; PMID: 19809478).
		Cybrids with high heteroplasmy levels (90%, 93%, 96%) were generated and showed a pattern consistent with patient fibroblasts, and tRNA tryptophan levels were reduced in cybrids to 33% (PS3_supporting; PMID: 19809478). PubMed:19809478

Not Met criteria codes

PS4	✖	The m.5556G>A variant in MT-TW has been reported in one individual with mitochondrial disease to date (PMID: 19809478). This was a girl with feeding difficulty and reflux shortly after birth and developmental regression beginning at age seven months. She also had constipation, failure to thrive, and died at 13 months due to respiratory insufficiency. She had metabolic acidosis and elevated blood and cerebrospinal fluid lactate. There was reduced activity of complexes I, III, and IV in skeletal muscle and fibroblasts, and reduced levels of fully assembled complexes I, III, IV, and V in fibroblast cell line. Mitochondrial protein synthesis and tRNA tryptophan was reduced in fibroblasts. The variant was present at 92% heteroplasmy in fibroblasts and 93% in skeletal muscle.
PP3	✖	In silico prediction tools are conflicting as the computational predictor MitoTIP suggests this variant is tolerated (44.5 percentile) but HmtVAR predicts it to be deleterious (score of 0.85).

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.5556G>A	Likely Pathogenic	Mitochondrial Disease	2025-07-16	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-TW
View	m.5556G>A	Likely Pathogenic	Mitochondrial Disease	2025-07-16	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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