The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NC_012920.1:m.4298G>A

Version: 1.1

CA913177648

689874 (ClinVar)

Gene: MT-TI (HGNC:4565)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 81c411b2-d088-4403-b4e1-80a42a98c302
Approved on: 2022-12-12
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HGVS expressions

NC_012920.1:m.4298G>A
J01415.2:m.4298G>A

Uncertain Significance

Met criteria codes 4

PS4_Supporting PS3_Supporting PM2_Supporting PP3

Not Met criteria codes 2

PM6 PP1

Evidence Links 0

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.4298G>A variant in MT-TI has been reported in two unrelated adults with primary mitochondrial disease. Chronic progressive external ophthalmoplegia (CPEO) and multiple sclerosis (MS) were seen in one individual (PMID: 9473477) and the second individual had rhabdomyolysis, myoglobinuria, and myalgia after fasting or exercise in addition to muscle weakness and unstable gait (PMID: 16120360). This variant was seen in varying degrees of heteroplasmy in these individuals in muscle, urine, and hair roots by PCR/RFLP, but was not observed in blood (PS4_supporting). Family member testing was performed in one case and the variant was undetectable in the proband's mother's blood, however the variant was also undetectable in the proband's blood precluding confirmation of a de novo occurrence (PMID: 16120360). There are no large families reported in the medical literature to consider for evidence of segregation. The computational predictor MitoTIP suggests this variant is pathogenic, scoring in the 63.5 percentile; HmtVAR also predicts it to be pathogenic, scoring in the 75.0 percentile (PP3). The m.4298G>A variant is absent in the GenBank dataset, the Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Single-fiber testing (PMID: 9473477) showed 78% heteroplasmy in COX-negative fibers and 27% in COX-positive fibers.

Aminoacylation assays showed that the capacity for aminoacylation of tRNAs with this variant was virtually nil (<0.1%) and the observed aminoacylation deficiency was rescued by an engineered compensatory variant (PMID: 12655007). This and other results led the authors to propose that the functional defect caused by this mutation is due to fragility of the tRNA structure (PS3_supporting). In summary, this variant meets criteria to be classified as uncertain significance for primary mitochondrial disease inherited in a mitochondrial manner. We note that two experts on this panel felt likely pathogenic was a more appropriate classification given the functional evidence of impact however the majority agreed with uncertain significance. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on December 12, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS4_supporting, PS3_supporting, PP3, PM2_supporting.

Met criteria codes

PS4_Supporting	✔	The m.4298G>A variant in MT-TI has been reported in two unrelated adults with primary mitochondrial disease. Chronic progressive external ophthalmoplegia (CPEO) and multiple sclerosis (MS) were seen in one individual (PMID: 9473477) and the second individual had rhabdomyolysis, myoglobinuria, and myalgia after fasting or exercise in addition to muscle weakness and unstable gait (PMID: 16120360). This variant was seen in varying degrees of heteroplasmy in these individuals in muscle, urine, and hair roots by PCR/RFLP, but was not observed in blood (PS4_supporting).
PS3_Supporting	✔	Single-fiber testing (PMID: 9473477) showed 78% heteroplasmy in COX-negative fibers and 27% in COX-positive fibers. Aminoacylation assays showed that the capacity for aminoacylation of tRNAs with this variant was virtually nil (<0.1%) and the observed aminoacylation deficiency was rescued by an engineered compensatory variant (PMID: 12655007). This and other results led the authors to propose that the functional defect caused by this mutation is due to fragility of the tRNA structure (PS3_supporting).
PM2_Supporting	✔	The m.4298G>A variant is absent in the GenBank dataset, the Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic, scoring in the 63.5 percentile; HmtVAR also predicts it to be pathogenic, scoring in the 75.0 percentile (PP3).

Not Met criteria codes

PM6	✖	Family member testing was performed in one case and the variant was undetectable in the proband’s mother’s blood, however the variant was also undetectable in the proband’s blood precluding confirmation of a de novo occurrence (PMID: 16120360).
PP1	✖	There are no large families reported in the medical literature to consider for evidence of segregation.

Curation History

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