

Variant: *NC\_012920.1(MT-TT):m.15915G>A*

Version: 1.0

[CA913175191](#)

[690233 \(ClinVar\)](#)

**Gene:** N/A

**Condition:** mitochondrial disease ([MONDO:0044970](#))

**Inheritance Mode:** Mitochondrial inheritance

**UUID:** f4d748df-6d55-4a70-8801-ed14337c7572

**Approved on:** 2024-03-26

**Published on:** 2025-10-29

### *HGVS expressions*

**NC\_012920.1:m.15915G>A**

J01415.2:m.15915G>A

Uncertain Significance

Met criteria codes **3**

PS3\_Supporting

PM2\_Supporting

PP3

Not Met criteria codes **1**

PM6

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.15915G>A variant in MT-TT has been reported in one individual with primary mitochondrial disease (PMID: 8769114). This individual had myopathy, muscle wasting, seizures, myoclonus, headaches, vomiting, progressive hearing loss, cataracts, hypogonadism, and short stature. He had elevated blood and cerebrospinal fluid lactate levels. Brain imaging showed diffuse cerebellar and cerebral atrophy and calcifications in putamen, globus pallidus, caudate head, and dentate nucleus. Muscle biopsy showed moderate variation in fiber size, marked type 2B fiber atrophy, few ragged red fibers, focal COX deficiency, and some SDH-reactive blood vessels. The variant was present at 74% heteroplasmy in muscle, 32% in fibroblasts, and 18% in blood. The variant was not detected in blood from the mother and brother, however technology at the time was limited in detecting low heteroplasmy levels. This variant is absent in the MITOMAP GenBank sequences and gnomAD v3.1.2, and there is one heteroplasmic occurrence in the Helix dataset (PM2\_supporting). MitoTIP predicts the variant is possible pathogenic (73.7 percentile) and HmtVAR predicts the variant is pathogenic (0.55, PP3). Functional characterization of the mutant tRNA suggest the variant changes the tRNA conformation, reduces the stability of the tRNA, reduces charging capacity of the

tRNA, and affects modification of the tRNA (PMID: 29648639, PS3\_supporting). 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 March 26, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM2\_supporting, PP3, PS3\_supporting.

#### Met criteria codes

- PS3\_Supporting**   Functional characterization of the mutant tRNA suggest the variant changes the tRNA conformation, reduces the stability of the tRNA, reduces charging capacity of the tRNA, and affects modification of the tRNA (PMID: 29648639, PS3\_supporting).
- Functional characterization of the mutant tRNA suggest the variant changes the tRNA conformation, reduces the stability of the tRNA, reduces charging capacity of the tRNA, and affects modification of the tRNA (PMID: 29648639, PS3\_supporting). [PubMed:29648639](#) 
- PM2\_Supporting**   This variant is absent in the MITOMAP GenBank sequences and gnomAD v3.1.2, and there is one heteroplasmic occurrence in the Helix dataset (PM2\_supporting).
- PP3**   MitoTIP predicts the variant is possible pathogenic (73.7 percentile) and HmtVAR predicts the variant is pathogenic (0.55, PP3).

#### Not Met criteria codes

- PM6**   The variant was not detected in blood from the mother and brother, however technology at the time was limited in detecting low heteroplasmy levels.

Curation History 

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See Report	Preferred Variant Title	Classification ⓘ	Condition	Published Date	Version ⓘ	Criteria Specification	Gene
<a href="#">View</a>	NC_012920.1(MT-TT):m.15915G>A	Uncertain Significance	Mitochondrial Disease <a href="#">↗</a>	2025-10-29	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA <a href="#">↗</a>	MT-TT <a href="#">↗</a>
<a href="#">View</a>	NC_012920.1(MT-TT):m.15915G>A	Uncertain Significance	Mitochondrial Disease <a href="#">↗</a>	2025-10-29	1.0	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA <a href="#">↗</a>	N/A

Showing 1 to 2 of 2 rows

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