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(MT-CYB):m.12276G>A

Version: 1.1

CA913169952

690181 (ClinVar)

Gene: MT-TL2 (HGNC:4568)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 7f29b46e-3ca2-469f-84af-88e03428335a
Approved on: 2022-11-30
Published on: 2023-01-10

HGVS expressions

NC_012920.1:m.12276G>A
J01415.2:m.12276G>A

Likely Pathogenic

Met criteria codes 5

PM6_Supporting | PP3 | PS4_Moderate | PS3_Supporting | PM2_Supporting

Evidence Links 2

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.12276G>A variant in MT-TL2 has been reported in four unrelated individuals with primary mitochondrial disease. Chronic progressive external ophthalmoplegia and myopathy were seen in three cases (PMIDs: 15649400, 15591266, 23847141), and two of these cases had pigmentary retinopathy (PMIDs: 15649400, 23847141). The fourth case had a progressive encephalopathy (PMID: 20022607). Muscle biopsies in affected individuals showed ragged red fibers, COX-negative fibers, and normal to reduced respiratory chain enzyme activities. Heteroplasmy levels were consistently highest in muscle, ranging from 18-81%, and were low (6-8%) to undetectable in other tissues (PS4_moderate, PMIDs: 15649400, 15591266, 23847141, 20022607). The variant was confirmed to have occurred de novo in one of the reported individuals (variant absent in blood and urine of healthy mother and sister, PMID: 20022607; PM6_supporting). There are no large families reported in the medical literature with testing performed to consider for evidence of segregation. The computational predictor MitoTIP suggests this variant is pathogenic (74.7 percentile) and HmtVAR predicts it to be pathogenic score of 0.65 (PP3). This variant is absent in the Helix dataset and gnomAD v3.1.2, and the single occurrence in the GenBank dataset is from an affected individual

(PM2_supporting). Single fiber testing was performed in two of the four reported cases (PS3_supporting). In one case, fibers with <75% of the variant exhibited normal COX/SDH ratios and fibers with 80% or higher had severe deficiency of COX activity (PMID: 15591266). In another individual (PMID: 20022607), COX-deficient fibers had ~80% heteroplasmy and COX-positive fibers had ~25% heteroplasmy, a statistically significant difference (p<0.001). 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 November 30, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_moderate, PM6_supporting, PM2_supporting, PP3, PS3_supporting.

Met criteria codes

PM6_Supporting	✔	The variant was confirmed to have occurred de novo in one of the reported individuals (variant absent in blood and urine of healthy mother and sister; PMID: 20022607, PM6_supporting).
PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic (74.7 percentile) and HmtVAR predicts it to be pathogenic score of 0.65 (PP3).
PS4_Moderate	✔	The m.12276G>A variant in MT-TL2 has been reported in four unrelated individuals with primary mitochondrial disease. Chronic progressive external ophthalmoplegia and myopathy were seen in three cases (PMIDs: 15649400, 15591266, 23847141), and two of these cases had pigmentary retinopathy (PMIDs: 15649400, 23847141). The fourth case had a progressive encephalopathy (PMID: 20022607). Muscle biopsies in affected individuals showed ragged red fibers, COX-negative fibers, and normal to reduced respiratory chain enzyme activities. Heteroplasmy levels were consistently highest in muscle, ranging from 18-81%, and were low (6-8%) to undetectable in other tissues (PS4_moderate, PMIDs: 15649400, 15591266, 23847141, 20022607).
PS3_Supporting	✔	Fibers with <75% of variant exhibited normal COX/SDH ratios. Fibers with 80% or higher had severe deficiency of COX activity (PMID: 15591266). In another study (PMID: 20022607), COX-deficient fibers had ~80% heteroplasmy and COX-positive fibers had ~25% heteroplasmy, a statistically significant difference (p<0.001). COX-deficient fibers had ~80% heteroplasmy. COX-positive fibers had ~25% heteroplasmy. This is a statistically significant difference (p<0.001). PubMed:20022607 Fibers with <75% of variant exhibited normal COX/SDH ratios. Fibers with 80% or higher had severe deficiency of COX activity. PubMed:15591266
PM2_Supporting	✔	This variant is absent in the Helix dataset and gnomAD v3.1.2, and the single occurrence in the GenBank dataset is from an affected individual (PM2_supporting).

Curation History

Showing 1 to 2 of 2 rows