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-TL1):m.3274A>G

Version: 1.1

CA120568

9598 (ClinVar)

Gene: MT-TL1 (HGNC:4567)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 895befe8-a07c-4951-9ef0-a20ea6591579
Approved on: 2024-04-23
Published on: 2024-08-08

HGVS expressions

NC_012920.1:m.3274A>G
J01415.2:m.3274A>G

Uncertain Significance

Met criteria codes 3

PM2_Supporting PS3_Supporting 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.3274A>G in MT-TL1 has been reported in one individual to date, in a man with a progressive neuropsychiatric disorder and multisystem organ involvement. At 12 years old, he had a decline in school performance. By his late 20s, he experienced acute psychotic symptoms and depression. He also had bilateral hearing loss, gait instability, and bilateral dysdiadokinesis. By his early 30s, he had cataracts, retinal degeneration, muscle weakness, ataxic gait, dysarthria, intention tremor, and dysmetria. Brain MRIs showed progressive cerebral and cerebellar atrophy and T2 hyperintense lesions in the basal ganglia. He had elevated blood and cerebrospinal fluid lactate. Muscle biopsy showed increased central nuclei and ragged red fibers, with reduced complex I activity (53% of lowest norm). The variant was present at 25% in muscle and undetectable in blood (PMID: 11723298). The variant was absent in blood from three healthy maternal family members, but this cannot be considered evidence of de novo status as the variant was also absent in the proband's blood. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Single fiber testing showed higher levels of the variant in ragged red fibers (55 ± 26.1%; N=22; mutant mtDNA found in every fiber) than in normal fibers (14 ± 25.7%; N=16; mutant

mtDNA found in 7/16 fibers), p<0.001 (PS3_supporting, PMID: 11723298). The computational predictor MitoTIP suggests this variant is pathogenic (77.1 percentile) and HmtVAR predicts it to be pathogenic score of 0.55 (PP3). 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 April 23, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS3_supporting, PM2_supporting, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PS3_Supporting	✔	Single fiber testing showed higher levels of the variant in ragged red fibers (55 ± 26.1%; N=22; mutant mtDNA found in every fiber) than in normal fibers (14 ± 25.7%; N=16; mutant mtDNA found in 7/16 fibers), p<0.001 (PS3_supporting, PMID: 11723298).
		Single fiber testing showed higher levels of the variant in ragged red fibers (55 ± 26.1%; N=22; mutant mtDNA found in every fiber) than in normal fibers (14 ± 25.7%; N=16; mutant mtDNA found in 7/16 fibers), p<0.001 (PS3_supporting, PMID: 11723298). PubMed:11723298
PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic (77.1 percentile) and HmtVAR predicts it to be pathogenic score of 0.55 (PP3).

Curation History

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