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: m.14674T>C

Version: 1.1

CA120581

9618 (ClinVar)

Gene: MT-TE (HGNC:4556)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: c3041f19-42e2-4b31-b407-b0847507f476
Approved on: 2023-01-23
Published on: 2023-03-14

HGVS expressions

NC_012920.1:m.14674T>C
J01415.2:m.14674T>C

Likely Pathogenic

Met criteria codes 3

PS3_Supporting PS4 PP3

Not Met criteria codes 5

BP4 PS2 PM6 PM2 PP1

Evidence Links 3

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.14674T>C variant in MT-TE has been reported in at least 30 cases from 25 kindreds with primary mitochondrial disease. This variant is most commonly associated with reversible infantile respiratory chain deficiency (RIRCD), and has an estimated penetrance of 30% in reported families. The variant has been reported in the homoplasmic state in both affected and unaffected family members. There is one report of a heteroplasmic occurrence (90%) in a healthy mother. Age of onset in affected individuals generally ranged from birth to six weeks old, however there have been reports of weak fetal movements and one report with onset at four years old. Features include severe myopathy, feeding difficulty, and hypotonia that gradually improve over time, however mild myopathic features persist in many reported cases. Muscle biopsy findings in affected individuals include ragged red fibers, COX deficiency, and reduced respiratory chain enzyme activities in early biopsies that normalize on subsequent biopsies (PS4; PMIDs: 8155739, 19720722, 21194154, 21931168, 31333056, 33832841, 34732400, 34806237). There are no reported de novo occurrences of this variant to our knowledge. This variant is present in population databases which is to be expected given the known reduced penetrance of this variant (Mitomap: 56,910 sequences,

AF=0.018%; Helix: 195,983 sequences, AF=0.006%; gnomAD v3.1.2: 56,429 sequences, AF=0.004% - homoplasmic in two individuals and heteroplasmic in three individuals). The computational predictor MitoTIP suggests this variant is pathogenic (29.4 percentile but confirmed pathogenicity) and HmtVAR predicts it to be pathogenic score of 0.8 (PP3). Several studies in skeletal muscle and primary cell cultures of affected individuals (PMID: 19720722), cybrids (PMID: 21194154), and transcriptome and proteomic analyses (PMID: 33128823) support the functional impact of this variant (PS3_supporting). 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 January 23, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4, PP3, PS3_supporting.

Met criteria codes

PS3_Supporting ✔

Several studies in skeletal muscle and primary cell cultures of affected individuals (PMID: 19720722), cybrids (PMID: 21194154), and transcriptome and proteomic analyses (PMID: 33128823) support the functional impact of this variant (PS3_supporting).

Cybrids generated from patient 6 (included under PS4) showed normal aminoacylation of tRNAGlu. Respiratory chain enzyme activities were decreased for complexes I, III, and IV; and BN-PAGE showed a severe decrease in the amounts of CI and CIV. PubMed:21194154

Several additional cases were reported in this publication, and modifiers for reduced penetrance discussed that were identified by transcriptome and proteomic analysis. Integrated stress response associated with increased FGF21 and GDF15 (authors found these were profoundly increased in muscle in acute phase and normalized after recovery) expression enhances the metabolism modulated by serine biosynthesis, one carbon metabolism, TCA lipid oxidation, and amino acid availability. mTOR activation then leads to increased mitochondrial biogenesis. They also compared expression of patients with digenic EARS2 variants vs those without these and found significantly lower expression of mtDNA-encoded proteins. PubMed:33128823

Northern blotting of skeletal muscle of Patients 7, 11 and 14 and primary cell cultures of Patients 7 and 14 showed that that the steady-state level of mt-tRNAGlu was significantly decreased compared to controls, with the most severe decrease (16-30% of controls) seen in muscle taken between 1-3 months old. Muscle taken after recovery had less severely decreased steady-state levels (30-60% controls). Immunoblotting with monoclonal antibodies against mitochondrial-encoded COX and complex I subunits showed markedly decreased levels in early biopsies, when the children showed severe symptoms and this normalized in biopsies after recovery (and was normal in biopsies from healthy mothers). PubMed:19720722

PS4 ✔

The m.14674T>C variant in MT-TE has been reported in at least 30 cases from 25 kindreds. This variant is most commonly associated with reversible infantile respiratory chain deficiency (RIRCD), and has an estimated penetrance of 30% in reported families. The variant has been reported in the homoplasmic state in both affected and unaffected family members. There is one report of a heteroplasmic occurrence (90%) in a healthy mother. Age of onset in affected individuals generally ranges from birth to six weeks old, however there have been reports of weak fetal movements and one report with onset at four years old. Features include severe myopathy, feeding difficulty, and hypotonia that gradually improves overtime however mild myopathic features persist in many reported cases. Muscle biopsy findings in affected individuals include ragged red fibers, COX deficiency, and reduced respiratory chain enzyme activities in early biopsies that normalize on subsequent biopsies (PS4; PMIDs: 8155739, 19720722, 21194154, 21931168, 31333056, 33832841, 34732400, 34806237).

PP3 ✔

The computational predictor MitoTIP suggests this variant is pathogenic (29.4 percentile but confirmed pathogenicity) and HmtVAR predicts it to be pathogenic score of 0.8 (PP3).

Not Met criteria codes

BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	There are no reported de novo occurrences of this variant to our knowledge.
PM6		✖	There are no reported de novo occurrences of this variant to our knowledge.
PM2		✖	This variant is present in population databases (Mitomap: 56,910 sequences, AF=0.018%; Helix: 195,983 sequences, AF=0.006%; gnomAD v3.1.2: 56,429 sequences, AF=0.004% - homoplasmic in two individuals and heteroplasmic in three individuals). Given the frequency of this variant, it does not meet PM2 criterion.
PP1		✖	This variant has been seen in the homoplasmic state in affected and unaffected family members.

Curation History

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