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Variant: m.586G>A

Version: 1.1

CA128831

30005 (ClinVar)

Gene: MT-TF (HGNC:4558)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: f333f6f6-be97-4d97-899b-db6db92f26e8
Approved on: 2024/6/10
Published on: 2024/12/6

HGVS expressions

NC_012920.1:m.586G>A
J01415.2:m.586G>A

Uncertain Significance

Met criteria codes 5

PM2_Supporting PM6_Supporting PP3 PS4_Supporting PS3_Supporting

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.586G>A variant in MT-TF has been reported in two unrelated individuals with primary mitochondrial disease (PS4_supporting; PMIDs: 21060018, 31463198). One individual was a 57-year-old woman with hearing loss onset in her mid 40s that progressed to profound hearing loss in her 50s, myopathy and progressive exercise intolerance with reduced mobility and falls onset in her late 40s, and spasticity, facial grimacing, dementia, and psychiatric manifestations in her mid 50s (PMID: 21060018). Brain imaging showed generalized cerebral, cerebellar, and brainstem atrophy. Cerebrospinal fluid lactate was elevated. Muscle biopsy showed ragged red fibers and COX-deficient fibers. The variant was present in muscle at 85% heteroplasmy, urinary epithelia at 29%, and blood at 3%. Her mother had died however DNA from paraffin-embedded breast tissue was obtained and revealed the variant at 13% heteroplasmy. The other individual was a 14-year-old boy with exercise intolerance and muscle weakness that followed a stable course (PMID: 31463198). Brain imaging was normal. Lactate was elevated in blood. Muscle biopsy showed ragged red fibers, COX-negative fibers, and mitochondrial respiratory chain complexes I, III, and IV deficiency. The variant was present at >90% in muscle, 40% in urinary epithelia, and was present at trace levels in

blood. The variant was undetectable in his mother's blood and urinary epithelia (PM6_supporting; PMID: 31463198). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). The computational predictor MitoTIP suggests this variant is pathogenic (89.7 percentile) and HmtVAR predicts it to be pathogenic score of 0.6 (PP3). Single fiber testing showed higher levels of the variant in COX-deficient fibers (99.4±0.2%, n=11) than in COX-positive fibers (72.1±8.5%, n=9; p<0.001; PS3_supporting, PMID: 21060018). 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 June 10, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_supporting, PM6_supporting, PP3, PS3_supporting, PM2_supporting.

Met criteria codes

PM2_Supporting ✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PM6_Supporting ✔	The variant was present at >90% in muscle, 40% in urinary epithelia, and was present at trace levels in blood from the proband. The variant was undetectable in his mother's blood and urinary epithelia (PM6_supporting; PMID: 31463198).
PP3 ✔	The computational predictor MitoTIP suggests this variant is pathogenic (89.7 percentile) and HmtVAR predicts it to be pathogenic score of 0.6 (PP3).
PS4_Supporting ✔	The m.586G>A variant in MT-TF has been reported in two unrelated individuals with primary mitochondrial disease. One individual was a 57-year-old woman with hearing loss onset in her mid 40s that progressed to profound hearing loss in her 50s, myopathy and progressive exercise intolerance with reduced mobility and falls onset in her late 40s, and spasticity, facial grimacing, dementia, and psychiatric manifestations in her mid 50s (PMID: 21060018). Brain imaging showed generalized cerebral, cerebellar, and brainstem atrophy. Cerebrospinal fluid lactate was elevated. Muscle biopsy showed ragged red fibers and COX-deficient fibers. The variant was present in muscle at 85% heteroplasmy, urinary epithelia at 29%, and blood at 3%. Her mother had died however DNA from paraffin-embedded breast tissue was obtained and revealed the variant at 13% heteroplasmy. The other individual was a 14-year-old boy with exercise intolerance and muscle weakness that was following a stable course. Brain imaging was normal (PMID: 31463198). Lactate was elevated in blood. Muscle biopsy showed ragged red fibers, COX-negative fibers, and mitochondrial respiratory chain complex I, III, and IV deficiency.
PS3_Supporting ✔	Single fiber testing showed higher levels of the variant in COX-deficient fibers (99.4%) than in COX-positive fibers (72.1%; PS3_supporting, PMID: 21060018). In a single fiber study, significantly higher levels of the m.586G>A mutation were present in COX-deficient fibers (99.4%) than in COX-positive fibers (72.1%) PubMed:21060018

Curation History

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