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Variant: NC_012920.1(MT-TL1):m.3252A>G

Version: 1.1

CA120564

9594 (ClinVar)

Gene: MT-TL1 (HGNC:4567)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 377f8580-a450-4ddc-8065-cec5821c1c42
Approved on: 2024-09-09
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HGVS expressions

NC_012920.1:m.3252A>G
J01415.2:m.3252A>G

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PS2_Supporting PS4_Moderate PP1_Moderate

Not Met criteria codes 2

PS3 PM6

Evidence Links 0

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.3252A>G variant in MT-TL1 has been reported in five unrelated families with primary mitochondrial disease (PS4_moderate). Some affected individuals had features consistent with myoclonic epilepsy with ragged red fibers (MERRF) and/or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Other manifestations include intellectual disability, pigmentary retinopathy, diabetes, dementia, renal failure, heart block, and hypoparathyroidism; and muscle biopsies showed ragged red fibers and complex I deficiency. Heteroplasmy levels ranged from 18% to greater than 90% in affected individuals (PMID: 8111377; of note, two cases were included in manuscripts without a PMID: Seed et al., 2021, Tan et al., 2023; and two cases were provided by Expert Panel members). The variant segregated with disease manifestations in two families (PP1_moderate). In one, the proband had MELAS and had the variant present at 30% heteroplasmy in blood, 19% in lymphoblasts, and 76% in muscle. The mother had progressive generalized weakness, spastic paraparesis, and dysarthria onset in her 40s and died at 58 years following a stroke-like episode, and was found to have the variant present at 50% heteroplasmy in muscle (PMID: 8111377). In one of the cases provided by an Expert Panel member, the proband

had the variant present at >90% heteroplasmy. The less severely affected mother had the variant present at 55% in urine, 40% in buccal, and 18% in blood. The variant was present in the maternal grandmother at 19% in buccal sample, and at lower heteroplasmy levels in a maternal uncle with hearing loss. This variant occurred de novo in one of the reported individuals (absent in blood from mother; PS2_supporting, Tan et al., 2023). 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 and HmtVAR predicts it to be pathogenic score of 0.5 (PP3). There are no cybrids, single fiber studies, or other functional assays reported on this variant. 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 September 9, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_moderate, PP1_moderate, PS2_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).
PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic and HmtVAR predicts it to be pathogenic score of 0.5 (PP3).
PS2_Supporting	✔	This variant occurred de novo in one of the reported individuals (absent in blood from mother; PS2_supporting, Tan et al., 2023).
PS4_Moderate	✔	The m.3252A>G variant in MT-TL1 has been reported in five unrelated families with primary mitochondrial disease (PS4_moderate). Some affected individuals had features consistent with myoclonic epilepsy with ragged red fibers (MERRF) and/or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Other manifestations include intellectual disability, pigmentary retinopathy, diabetes, dementia, renal failure, heart block, and hypoparathyroidism; and muscle biopsies showed ragged red fibers and complex I deficiency. Heteroplasmy levels ranged from 18% to greater than 90% in affected individuals (PMID: 8111377; of note, two cases were included in manuscripts without a PMID: Seed et al., 2021, Tan et al., 2023; and two cases were provided by Expert Panel members).
PP1_Moderate	✔	The variant segregated with disease manifestations in two families (PP1_moderate). In one, the proband had MELAS and had the variant present at 30% heteroplasmy in blood, 19% in lymphoblasts, and 76% in muscle. The mother had progressive generalized weakness, spastic paraparesis, and dysarthria onset in her 40s and died at 58 years following a stroke like episode, and was found to have the variant present at 50% heteroplasmy in muscle (PMID: 8111377). In one of the cases provided by an Expert Panel member, the proband had the variant present at >90% heteroplasmy. The less severely affected mother had the variant present at 55% in urine, 40% in buccal, and 18% in blood. The variant was present in the maternal grandmother at 19% in buccal sample. The variant was also present at lower heteroplasmy levels in a maternal uncle with hearing loss.

Not Met criteria codes

PS3	✖	There are no cybrids, single fiber studies, or other functional assays reported on this variant.
PM6	✖	There are no reported de novo occurrences of this variant to our knowledge.

Curation History

Showing 1 to 2 of 2 rows