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Variant: NC_012920.1(MT-TK):m.8342G>A

Version: 1.1

CA120556

9582 (ClinVar)

Gene: MT-TK (HGNC:4566)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 3c7177ea-fdb9-4519-bf42-32453870526a
Approved on: 2023/7/24
Published on: 2025/6/3

HGVS expressions

NC_012920.1:m.8342G>A
J01415.2:m.8342G>A

Uncertain Significance

Met criteria codes 2

PP3 PM2_Supporting

Not Met criteria codes 4

PS2 PS4 PP1 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.8342G>A variant in MT-TK has been reported in one individual with primary mitochondrial disease to date (PMID: 10220860), in a woman with ophthalmoplegia, ptosis, fatigue, muscle weakness, resting tremor, and myoclonic jerks. Muscle biopsy showed COX-negative fibers and decreased electron transport chain enzyme activities. The variant was present at 80% heteroplasmy in muscle and was undetectable in blood lymphocytes. The variant was also undetectable in blood lymphocytes from her asymptomatic mother, maternal aunt, and daughter. As the variant was also undetectable in this tissue in the proband, this cannot be considered a confirmed de novo occurrence. Single fiber testing in the proband showed higher levels of the variant in COX negative fibers (74%, n=26) than in COX positive fibers (53%, n=28), p<0.0003 (PS3_supporting, PMID: 10220860). There are no cybrids or other functional analyses reported for this variant. There is one additional reported individual with the variant in the medical literature, however the heteroplasmy levels are too low (3-4%) to be causative of the clinical features noted (febrile infection-related epilepsy syndrome, or FIRES; PMID: 37077567). This variant is absent in the MITOMAP GenBank dataset and gnomAD v3.1.2, and there is one heteroplasmic occurrence in the Helix dataset

(PM2_supporting). The computational predictor MitoTIP suggests this variant is pathogenic (77.2 percentile) and HmtVAR predicts it to be pathogenic score of 0.65 (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 July 24, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS3_supporting, PM2_supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic (77.2 percentile) and HmtVAR predicts it to be pathogenic score of 0.65 (PP3).
PM2_Supporting	✔	This variant is absent in the MITOMAP GenBank dataset and gnomAD v3.1.2, and there is one heteroplasmic occurrence in the Helix dataset (PM2_supporting).

Not Met criteria codes

PS2	✖	The variant was also undetectable in blood lymphocytes from her asymptomatic mother, maternal aunt, and daughter. The variant was also undetectable in the proband's blood.
PS4	✖	The m.8342G>A variant in MT-TK has been reported in one individual with primary mitochondrial disease to date (PMID: 10220860), in a woman with ophthalmoplegia, ptosis, fatigue, muscle weakness, resting tremor, and myoclonic jerks. Muscle biopsy showed COX-negative fibers and decreased electron transport chain enzyme activities. The variant was present at 80% heteroplasmy in muscle and was undetectable in blood lymphocytes. There is one additional reported individual with the variant in the medical literature, however the heteroplasmy levels are too low (3-4%) to be causative of the clinical features noted (febrile infection-related epilepsy syndrome, or FIRES; PMID: 37077567).
PP1	✖	The variant was also undetectable in blood lymphocytes from her asymptomatic mother, maternal aunt, and daughter.
PM6	✖	The variant was also undetectable in blood lymphocytes from her asymptomatic mother, maternal aunt, and daughter. The variant was also undetectable in the proband's blood.

Curation History

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