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Variant: m.8356T>C

Version: 1.1

CA120554

9580 (ClinVar)

Gene: MT-TK (HGNC:4566)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: c803d965-c7ab-4569-bee1-92a570eb1fc9
Approved on: 2023/3/13
Published on: 2023/3/14

HGVS expressions

NC_012920.1:m.8356T>C
J01415.2:m.8356T>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting | PP3 | PP1_Moderate | PS4_Supporting | PS3_Supporting

Not Met criteria codes 2

PM6 | PS2

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.8356T>C variant in MT-TK has been reported in at least 11 individuals from two kindreds with primary mitochondrial disease. Age of onset ranged from the first decade of life to adulthood. Features seen in affected individuals include myoclonic epilepsy with ragged red fibers (MERRF), ataxia, generalized seizures, hearing loss, and lactic acidosis. Heteroplasmy levels were consistently lower in blood and higher in muscle, ranging from 43.4% to homoplasmy (PMIDs: 8069654, 1361099; PS4_supporting). Of note, there is an additional family reported in the literature that was not considered for this variant curation given the presence of another pathogenic variant, m.3243A>G. These individuals had features similar to those seen in individuals with m.8356T>C, as well as features classic for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS; PMID: 20610441). This variant segregated with disease manifestations in multiple members of one family reported (PMID: 8069654; PP1_moderate). There are no reported cases of de novo occurrences to our knowledge. The computational predictor MitoTIP suggests this variant impacts the function of this tRNA (88.8 percentile) as does HmtVar with a score of 0.75 (PP3). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2

(PM2_supporting). In cybrid cell lines homoplasmic for this variant, reduced oxygen consumption was reported, supporting the functional impact of this variant (PMID: 7739567; PS3_supporting). In summary, this variant meets criteria to be classified as likely pathogenic for primary mitochondrial disease inherited in a maternal manner. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on March 13, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS3_supporting, PS4_supporting, PP1_moderate, PP3, PM2_supporting.

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 impacts the function of this tRNA (88.8 percentile) as does HmtVar with a score of 0.75 (PP3).
PP1_Moderate	✔	This variant segregated with disease manifestations in multiple members of one family reported (PMID: 8069654; PP1_moderate).
PS4_Supporting	✔	The m.8356T>C variant in MT-TK has been reported in at least 11 individuals from two kindreds with primary mitochondrial disease. Age of onset ranged from the first decade of life to adulthood. Features seen in affected individuals include myoclonic epilepsy with ragged red fibers (MERRF), ataxia, generalized seizures, hearing loss, and lactic acidosis. Heteroplasmy levels were consistently lower in blood and higher in muscle, ranging from 43.4% to homoplasmy (PMIDs: 8069654, 1361099; PS4_supporting). Of note, there is an additional family reported in the literature that was not considered for this variant curation given the presence of another pathogenic variant, m.3243A>G. These individuals had features similar to those seen in individuals with m.8356T>C, as well as features classic for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS; PMID: 20610441).
PS3_Supporting	✔	In cybrid cell lines homoplasmic for this variant, reduced oxygen consumption was reported, supporting the functional impact of this variant (PMID: 7739567; PS3_supporting).

Not Met criteria codes

PM6	✖	There are no reported cases of de novo occurrences to our knowledge.
PS2	✖	There are no reported cases of de novo occurrences to our knowledge.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.8356T>C	Likely Pathogenic	Mitochondrial Disease	2023-03-14	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-TK
View	m.8356T>C	Likely Pathogenic	Mitochondrial Disease	2023-03-14	1.0	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	N/A

Showing 1 to 2 of 2 rows

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