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Variant: m.12258C>A

Version: 1.1

CA120544

9560 (ClinVar)

Gene: MT-TS2 (HGNC:4575)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 14123169-39c1-4a25-900a-e79c5ccae83a
Approved on: 2023/3/28
Published on: 2023/4/3

HGVS expressions

NC_012920.1:m.12258C>A
J01415.2:m.12258C>A

Likely Pathogenic

Met criteria codes 5

PP3 PM2_Supporting PS4_Supporting PS3_Supporting PP1_Moderate

Not Met criteria codes 6

PM6 BA1 BS1 BS3 BP4 PS2

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.12258C>A variant in MT-TS2 gene has been reported in two unrelated individuals with primary mitochondrial disease (PS4_supporting). Family members of both probands were also affected. The age of onset was in adulthood and ranged from the 20s to 60s. Features seen in affected individuals include diabetes, cataracts, retinitis pigmentosa, hearing loss, and cerebellar ataxia (PMIDs: 9792552, 10090882). This variant segregated with disease in multiple affected members in both families and several healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 10090882, 9792552). There are no reported de novo occurrences of this variant to our knowledge. There is one occurrence in population databases (one occurrence in Mitomap GenBank sequences, absent in gnomAD v3.1.2 and Helix dataset). Although there is one occurrence, the frequency is still low (PM2_supporting). The computational predictor MitoTIP suggests this variant is pathogenic (95.3 percentile) and HmtVAR predicts it to be pathogenic with a score of 0.4 (PP3). Single fiber studies support the functional impact of this variant (PS3_supporting) as the level of variant in COX-positive fibers ranged from 23-71%, while in COX-negative fibers was present at >85% heteroplasmy (PMID: 9792552). 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 March 28, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_supporting, PP1_moderate, PM2_supporting, PP3, PS3_supporting.

Met criteria codes

PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic (95.3 percentile) and HmtVAR predicts it to be pathogenic with a score of 0.4 (PP3).
PM2_Supporting	✔	There is one occurrence in population databases (one occurrence in Mitomap GenBank sequences, absent in gnomAD v3.1.2 and Helix dataset). Although there is one occurrence, the frequency is still low (PM2_supporting).
PS4_Supporting	✔	The m.12258C>A variant in MT-TS2 gene has been reported in two unrelated individuals with primary mitochondrial disease (PS4_supporting). Family members of both probands were also affected. The age of onset was in adulthood and ranged from the 20s to 60s. Features seen in affected individuals include diabetes, cataracts, retinitis pigmentosa, hearing loss, and cerebellar ataxia (PMIDs: 9792552, 10090882).
PS3_Supporting	✔	Single fiber studies support the functional impact of this variant (PS3_supporting) as the level of variant in COX-positive fibers ranged from 23-71%, while in COX-negative fibers was present at >85% heteroplasmy (PMID: 9792552). Single fiber studies showed the level of variant in COX-positive fibers ranged from 23-71%, while in COX-negative fibers was present at >85% heteroplasmy. PubMed:9792552
PP1_Moderate	✔	This variant segregated with disease in multiple affected members in multiple families and several healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 10090882, 9792552).

Not Met criteria codes

PM6	✖	There are no reported de novo occurrences of this variant to our knowledge.
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.12258C>A	Likely Pathogenic	Mitochondrial Disease	2023-04-03	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-TS2
View	m.12258C>A	Likely Pathogenic	Mitochondrial Disease	2023-04-03	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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