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Variant: m.11777C>A

Version: 1.1

CA120636

9711 (ClinVar)

Gene: MT-ND4 (HGNC:4538)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 5c213439-72fe-44b9-972e-30aec7a96987
Approved on: 2022/6/30
Published on: 2022/6/30

HGVS expressions

NC_012920.1:m.11777C>A
J01415.2:m.11777C>A
ENST00000361381.2:c.1018C>A

Likely Pathogenic

Met criteria codes 6

PS3_Supporting PS4_Moderate PM2_Supporting PP1 PP3 PM5

Not Met criteria codes 2

PS2 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.11777C>A (p.R340S) variant in MT-ND4 has been reported in at least eight unrelated individuals with primary mitochondrial disease and features including Leigh syndrome, stroke-like episodes, and cardiomyopathy (PS4_moderate; PMIDs: 12707444, 16120329, 15576045, 20502985, 24642831, 29428506). Ages of onset varied from the first few days of life to the 60s and heteroplasmy levels in affected individuals ranged from 50-93%. There is one report of the variant being absent in mother's blood (PMID: 16120329) however no additional tissues were tested and technology performed at the time of publication would not detect low heteroplasmy levels of the variant. This variant segregated with disease in one family, as two healthy family members had lower to undetectable levels of the variant (PP1; PMID: 20502985). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Another variant at this amino acid position leading to a different amino acid change is a known pathogenic variant – m.11778G>A (p.R340H, PM5). Cybrid studies supported the functional impact of this variant (PS3_supporting; PMID: 16120329). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.83 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). 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 Mitochondrial Disease Variant Curation Expert Panel on May 24, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_moderate, PP1, PS3_supporting, PM2_supporting, PM5, PP3.

Met criteria codes

PS3_Supporting	✔	Cybrid studies supported the functional impact of this variant (PS3_supporting; PMID: 16120329). Cybrid studies performed: "Primary cultures" from patients 1 and 2 (likely myoblasts in which decreased ATP synthesis was reported); ATP synthesis decreases with increasing heteroplasmy level.
PS4_Moderate	✔	The m.11777C>A (p.R340S) variant in MT-ND4 has been reported in at least eight unrelated individuals with primary mitochondrial disease and features including Leigh syndrome, stroke-like episodes, and cardiomyopathy (PS4_moderate; PMIDs: 12707444, 16120329, 15576045, 20502985, 24642831, 29428506). Ages of onset varied from the first few days of life to the 60s and heteroplasmy levels in affected individuals ranged from 50-93%.
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PP1	✔	This variant segregated with disease in one family, as two healthy family members had lower to undetectable levels of the variant (PP1_supporting; PMID: 20502985).
PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.83 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3).
PM5	✔	Another variant at this amino acid position leading to a different amino acid change is a known pathogenic variant – m.11778G>A (p.R340H, PM5).

Not Met criteria codes

PS2	✖	There is one report of the variant being absent in mother’s blood (PMID: 16120329) however no additional tissues were tested and technology performed at the time of publication would not detect low heteroplasmy levels of the variant.
PM6	✖	There is one report of the variant being absent in mother’s blood (PMID: 16120329) however no additional tissues were tested and technology performed at the time of publication would not detect low heteroplasmy levels of the variant.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.11777C>A	Likely Pathogenic	Mitochondrial Disease	2022-06-30	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-ND4
View	m.11777C>A	Likely Pathogenic	Mitochondrial Disease	2022-06-30	1.0	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	N/A

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