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Variant: m.4810G>A

Version: 1.1

CA120642

9720 (ClinVar)

Gene: MT-ND2 (HGNC:4536)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 7afe2fe4-ebc4-4f13-846c-740c7f4c4c1d
Approved on: 2023/10/9
Published on: 2024/8/15

HGVS expressions

NC_012920.1:m.4810G>A
J01415.2:m.4810G>A
ENST00000361453.3:c.341G>A

Likely Pathogenic

Met criteria codes 3

PVS1_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 4

PP1 PP3 PM6 PS4

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.4810G>A (p.W114*) variant in MT-ND2 has been reported in three individuals with primary mitochondrial disease to date. One individual was reported to have severe exercise intolerance, muscle weakness, myalgia, ophthalmoplegia, ptosis, elevated blood lactate, elevated CK, electromyography consistent with myopathy, and ragged red fibers on muscle biopsy (PMID: 15781840). Complex I activity was reduced in muscle. The variant was present at 94% heteroplasmy in muscle and was undetectable in blood. The two additional individuals reported had ophthalmoplegia and ptosis, however no additional details were provided (Roisin 2022, Newcastle University, https://theses.ncl.ac.uk/jspui/bitstream/10443/5737/1/Stout%20R%20B%202022.pdf). There are no reported de novo occurrences of this variant to our knowledge. There are no reports of large families with this variant segregating with disease. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). The transition at base position m.4810 causes a W114Ter change. This causes a significant truncation (67%) of the ND2 protein (PVS1_strong). Single fiber testing showed numerous ragged-red fibers with the variant present at a mean of 84.27% (n=15) compared to the variant being present at a mean heteroplasmy of 7.15% in the normal

fibers (n=14, PS3_supporting, PMID: 15781840). There are no in silico predictors for this type of variant in mitochondrial DNA. In summary, this variant meets criteria to be classified as likely pathogenic for primary mitochondrial disease inherited in a mitochondrial manner. We note that one expert on this panel felt uncertain significance was the more appropriate classification given only one case with clinical details has been reported and extensive functional validation is lacking. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on October 9, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM2_supporting, PS3_supporting, PVS1_strong.

Met criteria codes

PVS1_Strong	✔	The transition at base position m.4810 causes a W114Ter change. This causes a significant truncation (67%) of the ND2 protein (PVS1_strong).
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PS3_Supporting	✔	Single fiber testing showed numerous ragged-red fibers with the variant present at a mean of 84.27% (n=15) compared to the variant being present at a mean heteroplasmy of 7.15% in the normal fibers (n=14, PS3_supporting, PMID: 15781840).

Not Met criteria codes

PP1	✖	There are no reports of large families with this variant segregating with disease.
PP3	✖	There are no in silico predictors for this type of variant in mitochondrial DNA.
PM6	✖	There are no reported de novo occurrences of this variant to our knowledge.
PS4	✖	The m.4810G>A (p.W114*) variant in MT-ND2 has been reported in three individuals with primary mitochondrial disease to date. One individual was reported to have severe exercise intolerance, muscle weakness, myalgia, ophthalmoplegia, ptosis, elevated blood lactate, elevated CK, electromyography consistent with myopathy, and ragged red fibers on muscle biopsy (PMID: 15781840). Complex I activity was reduced in muscle. The variant was present at 94% heteroplasmy in muscle and was undetectable in blood. The two additional individuals reported had ophthalmoplegia and ptosis, however no additional details were provided (Roisin 2022, Newcastle University, https://theses.ncl.ac.uk/jspui/bitstream/10443/5737/1/Stout%20R%20B%202022.pdf).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.4810G>A	Likely Pathogenic	Mitochondrial Disease	2024-08-15	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-ND2
View	m.4810G>A	Likely Pathogenic	Mitochondrial Disease	2024-08-15	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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