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# *Variant: m.14453G>A*

Version: 1.1

*CA254853*

*9692 (ClinVar)*

**Gene**: MT-ND6 (HGNC:4541)
**Condition**: mitochondrial disease (MONDO:0044970)
**Inheritance Mode**: Mitochondrial inheritance
**UUID:** 0a3ba1f2-38e7-496b-9db7-ea9860bd412d
**Approved on**: 2022/6/30
**Published on**: 2022/6/30

## *HGVS expressions*

**NC_012920.1:m.14453G>A**
J01415.2:m.14453G>A
ENST00000361681.2:c.221C>T

**Likely Pathogenic**

**Met criteria codes** 4

PP3 PM2_Supporting PS4_Moderate PM6_Strong

**Not Met criteria codes** 2

PS3 PP1

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.14453G>A (p.A74V) variant in MT-ND6 has been reported in at least 10 individuals with primary mitochondrial disease from 10 families. Affected individuals had onset ranging from the first day of life to adulthood (all but one case had early childhood onset, however); and with features variably consistent with Leigh syndrome and MELAS (PS4_moderate; PMIDs: 34933128, 22947169, 33644659, 32552696, 24642831, 21364701, 11781695). Heteroplasmy levels ranged from 41-83%. There are at least five reports of de novo occurrences of this variant (PM6_strong, score 2.5; PMIDs: 34933128, 33644659, 24642831, 11781695). There is one report of this variant segregating with disease features as a healthy mother of a proband had the variant present at 2% in blood, however this does not meet criteria to apply PP1_supporting (at least two segregations). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). There are no cybrid studies, single fiber studies, or other functional assays reported for this variant. The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.81 (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 June 27, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_moderate, PM6_strong, PM2_supporting, PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✔ | The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.81 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). |
| **PM2_Supporting** | ✔ | This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). |
| **PS4_Moderate** | ✔ | The m.14453G>A (p.A74V) variant in MT-ND6 has been reported in at least 10 individuals with primary mitochondrial disease from 10 families. Affected individuals had onset ranging from the first day of life to adulthood (all but one case had early childhood onset, however); and with features variably consistent with Leigh syndrome and MELAS (PS4_moderate; PMIDs: 34933128, 22947169, 33644659, 32552696, 24642831, 21364701, 11781695). Heteroplasmy levels ranged from 41-83%. |
| **PM6_Strong** | ✔ | There are at least five reports of de novo occurrences of this variant (PM6_strong, score 2.5; PMIDs: 34933128, 33644659, 24642831, 11781695). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PS3** | ✖ | There are no cybrid studies, single fiber studies, or other functional assays reported for this variant. |
| **PP1** | ✖ | There is one report of this variant segregating with disease features as a healthy mother of a proband had the variant present at 2% in blood, however this does not meet criteria to apply PP1_supporting (at least two segregations). |

Curation History

Showing 1 to 2 of 2 rows

| See Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | m.14453G>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-ND6 |
| View | m.14453G>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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