The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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: 2022-06-30
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HGVS expressions

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

Likely Pathogenic

Met criteria codes 4

PS4_Moderate PM2_Supporting PM6_Strong PP3

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

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%.
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
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).
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).

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

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