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.14495A>G

Version: 1.1

CA340933

9691 (ClinVar)

Gene: MT-ND6 (HGNC:4541)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 1fc90c88-4e8f-4daa-a2b8-25cdd87f5188
Approved on: 2022-06-30
Published on: 2022-06-30

HGVS expressions

NC_012920.1:m.14495A>G
J01415.2:m.14495A>G
ENST00000361681.2:c.179T>C

Likely Pathogenic

Met criteria codes 4

PP3 PS4_Supporting PM2_Supporting PP1_Moderate

Not Met criteria codes 3

PS2 PS3 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.14495A>G (p.L60S) variant in MT-ND6 has been reported in five individuals from three families, all of whom had LHON (PS4_supporting; PMIDs: 2287992, 11133798). There are no reports of de novo occurrences to our knowledge. This variant segregated with disease in one family with LHON (all testing was performed in blood; affected individuals: proband/mother with variant present at 51% heteroplasmy, sons with variant at 93% and 92%; unaffected individuals: sister with variant at 23%, maternal niece with variant at 53%, and maternal nephew with variant at 37%; PP1_moderate; PMID: 11133798). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.87 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). There are no cybrid studies, single fiber studies, or other functional assays reported for this variant. This variant meets criteria to be classified as uncertain significance however, after extensive discussion, this Expert Panel elected to modify the classification to likely pathogenic given the strong segregation evidence and consistent phenotype in affected individuals. This classification was approved by the NICHD/NINDS U24 Mitochondrial Disease Variant Curation Expert

Panel on April 11, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_supporting, PP1_moderate, PM2_supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.87 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3).
PS4_Supporting	✔	The m.14495A>G (p.L60S) variant in MT-ND6 has been reported in five individuals from three families, all of whom had LHON (PS4_supporting; PMIDs: 2287992, 11133798).
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PP1_Moderate	✔	This variant segregated with disease in one family with LHON (all testing was performed in blood; affected individuals: proband/mother with variant present at 51% heteroplasmy, sons with variant at 93% and 92%; unaffected individuals: sister with variant at 23%, maternal niece with variant at 53%, and maternal nephew with variant at 37%; PP1_moderate; PMID: 11133798).

Not Met criteria codes

PS2	✖	There are no reports of de novo occurrences to our knowledge.
PS3	✖	There are no cybrid studies, single fiber studies, or other functional assays reported for this variant.
PM6	✖	There are no reports of de novo occurrences to our knowledge.

Curation History

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