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: NC_012920.1:m.13514A>G

Version: 1.1

CA345918

155889 (ClinVar)

Gene: MT-ND5 (HGNC:4540)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 965e5a6a-1c4b-4802-96d2-dd44fe81b825
Approved on: 2022-06-30
Published on: 2022-06-30

HGVS expressions

NC_012920.1:m.13514A>G
J01415.2:m.13514A>G
ENST00000361567.2:c.1178A>G

Likely Pathogenic

Met criteria codes 6

PP3 PM5 PS4_Moderate PS3_Supporting PM6_Supporting PM2_Supporting

Not Met criteria codes 4

PS1 PP1 PM4 PVS1

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.13514A>G (p.D393G) variant in MT-ND5 has been reported in at least 12 unrelated individuals with primary mitochondrial disease with onset ranging from childhood to adulthood and features variably consistent with Leigh syndrome and MELAS, as well as hypertrophic cardiomyopathy, optic atrophy, and neuropathy (PS4_moderate; PMIDs: 26341968, 25974876, 32504279, 20972245, 23847141, 21712854, 15576045, 14684687, 11198278). Heteroplasmy levels in affected individuals ranged from 55-70% in muscle, 12-55% in fibroblasts, 4-50% in blood, and 90% heart. This variant has been identified as a de novo occurrence in at least two probands with primary mitochondrial disease (PM6_supporting; PMIDs: 14684687, 11198278). There are no large families reported in the medical literature to consider for evidence of segregation. 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 classified as pathogenic by this Expert Panel – m.13513G>A (p. D393N, PM5). Cybrid studies showed a tight correlation between higher heteroplasmy level and lower complex I activity (PS3_supporting, PMID: 11198278). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.95

(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 3, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_moderate, PM6_supporting, PM2_supporting, PM5, PS3_supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.95 (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 classified as pathogenic by this Expert Panel – m.13513G>A (p. D393N, PM5).
PS4_Moderate	✔	The m.13514A>G (p.D393G) variant in MT-ND5 has been reported in at least 12 unrelated individuals with primary mitochondrial disease with onset ranging from childhood to adulthood and features variably consistent with Leigh syndrome and MELAS, as well as hypertrophic cardiomyopathy, optic atrophy, and neuropathy (PS4_moderate; PMIDs: 26341968, 25974876, 32504279, 20972245, 23847141, 21712854, 15576045, 14684687, 11198278). Heteroplasmy levels in affected individuals ranged from 55-70% in muscle, 12-55% in fibroblasts, 4-50% in blood, and 90% heart.
PS3_Supporting	✔	Cybrid studies showed a tight correlation between higher heteroplasmy level and lower complex I activity (PS3_supporting, PMID: 11198278).
PM6_Supporting	✔	This variant has been identified as a de novo occurrence in at least two probands with primary mitochondrial disease (PM6_supporting; PMIDs: 14684687, 11198278).
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).

Not Met criteria codes

PS1	✖	No other variants resulting in the same amino acid change have been reported.
PP1	✖	There are no large families reported in the medical literature to consider for evidence of segregation.
PM4	✖	This is a missense variant.
PVS1	✖	This is a missense variant.

Curation History

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