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.13094T>C

Version: 1.1

CA414816540

693516 (ClinVar)

Gene: MT-ND5 (HGNC:4540)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 2d75ef5b-05e0-47b1-a881-03bc267eeb5e
Approved on: 2022-07-25
Published on: 2022-09-02

HGVS expressions

NC_012920.1:m.13094T>C
J01415.2:m.13094T>C
ENST00000361567.2:c.758T>C

Pathogenic

Met criteria codes 6

PM2_Supporting | PP1_Moderate | PS4 | PP3 | PS3_Moderate | PM6_Supporting

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.13094T>C (p.V253A) variant in MT-ND5 has been reported in at least 25 individuals with primary mitochondrial disease from 18 families. Affected individuals had variable ages of onset (first months of life to childhood to 20s). Features included Leigh syndrome, MELAS, and LHON. Heteroplasmy levels were variable among tissues and affected individuals, however there are no reports of the variant being homoplasmic to our knowledge (PS4; PMIDs: 29506874, 29479304, 28429146, 23918514, 22577219, 20818383, 18977334; https://www.chop.edu/stories/melas-syndrome-ginas-and-her-familys-story). This variant segregated with disease in multiple families as healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 29506874, 29479304). This variant occurred de novo in at least two individuals (PM6_supporting, PMIDs: 23918514, 18977334). This variant is absent in population databases after removing sequences from individuals with mitochondrial disease (one occurrence in GenBank sequences is from an individual with mitochondrial disease; absent in gnomAD v3.1.2 and Helix dataset; PM2_supporting). Cybrid studies show two different classes of function defects (PS3_moderate): (1) complex I/CS activity ratio is highly correlated with the percentage of the variant and loss of ND5 is associated

with instability of the membrane arm of Complex I (PMID: 18977334) and (2) autophagy, determined as LC3B-II/Actin levels, was significantly increased in mutant cybrids (PMID: 29479304). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.89 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). In summary, this variant meets criteria to be classified as 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 July 25, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM2_supporting, PP3, PP1_moderate, PS3_moderate, PM6_supporting, PS4.

Met criteria codes

PM2_Supporting	✔	This variant is absent in population databases after removing sequences from individuals with mitochondrial disease (one occurrence in GenBank sequences is from an individual with mitochondrial disease; absent in gnomAD v3.1.2 and Helix dataset; PM2_supporting).
PP1_Moderate	✔	This variant segregated with disease in multiple families as healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 29506874, 29479304).
PS4	✔	The m.13094T>C (p.V253A) variant in MT-ND5 has been reported in at least 25 individuals with primary mitochondrial disease from 18 families. Affected individuals had variable ages of onset (first months of life to childhood to 20s). Features included Leigh syndrome, MELAS, and LHON. Heteroplasmy levels were variable among tissues and affected individuals, however there are no reports of the variant being homoplasmic to our knowledge (PS4; PMIDs: 29506874, 29479304, 28429146, 23918514, 22577219, 20818383, 18977334; https://www.chop.edu/stories/melas-syndrome-ginas-and-her-familys-story).
PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.89 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3).
PS3_Moderate	✔	Cybrid studies show two different classes of function defects (PS3_moderate): (1) complex I/CS activity ratio is highly correlated with the percentage of the variant and loss of ND5 is associated with instability of the membrane arm of Complex I (PMID: 18977334) and (2) autophagy, determined as LC3B-II/Actin levels, was significantly increased in mutant cybrids (PMID: 29479304).
PM6_Supporting	✔	This variant occurred de novo in at least two individuals (PM6_supporting, PMIDs: 23918514, 18977334).

Curation History

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