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(MT-ND1):m.3685T>C

Version: 1.1

CA414773304

1328561 (ClinVar)

Gene: MT-ND1 (HGNC:4535)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: dc5798a3-2e6a-4cc8-9444-6b958237144a
Approved on: 2024-10-28
Published on: 2025-08-07

HGVS expressions

NC_012920.1:m.3685T>C
J01415.2:m.3685T>C
ENST00000361390.2:c.379T>C

Uncertain Significance

Met criteria codes 3

PM2_Supporting PM6_Supporting PP3

Not Met criteria codes 3

PS2 PS3 PS4

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.3685T>C (p.Y127H) variant in MT-ND1 has been reported in one individual with primary mitochondrial disease to date, in a girl with Leigh syndrome (PMID: 35217561). She had developmental delay and regression, generalized tonic clonic seizures, and constipation. Brain MRI showed bilateral asymmetric basal ganglia signal hyperintensities and MRS showed elevated lactate and glucose in the basal ganglia. Labs showed elevated lactate, alanine, and GDF15. Complex I activity was slightly reduced in skin fibroblasts. The variant was present at 62.5% heteroplasmy in blood and was absent in her healthy mother's blood (PM6_supporting; PMID: 35217561). This variant is absent in the MITOMAP GenBank dataset, gnomAD v3.1.2, and the Helix dataset (PM2_supporting). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.750 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). There are no cybrids, single fiber studies, or other functional assays reported on this variant. In summary, this variant meets criteria to be classified as uncertain significance for primary mitochondrial disease inherited in a mitochondrial manner. This classification was approved by the

NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on October 28, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM6_supporting, PM2_supporting, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the MITOMAP GenBank dataset, gnomAD v3.1.2, and the Helix dataset (PM2_supporting).
PM6_Supporting	✔	The variant was present at 62.5% heteroplasmy in blood and was absent in her healthy mother's blood (PM6_supporting; PMID: 35217561).
PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.750 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3).

Not Met criteria codes

PS2	✖	The variant was present at 62.5% heteroplasmy in blood and was absent in her healthy mother's blood (PM6_supporting; PMID: 35217561).
PS3	✖	There are no cybrids, single fiber studies, or other functional assays reported on this variant.
PS4	✖	The m.3685T>C (p.Y127H) variant in MT-ND1 has been reported in one individual with primary mitochondrial disease to date, in a girl with Leigh syndrome (PMID: 35217561). She had developmental delay and regression, generalized tonic clonic seizures, and constipation. Brain MRI showed bilateral asymmetric basal ganglia signal hyperintensities and MRS showed elevated lactate and glucose in the basal ganglia. Labs showed elevated lactate, alanine, and GDF15. Complex I activity was slightly reduced in skin fibroblasts. The variant was present at 62.5% heteroplasmy in blood.

Curation History

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