Variant: NC_012920.1:m.10134C>A

Version: 3.1

CA270779

156375 (ClinVar)

Gene: MT-ND3 (HGNC:4537)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: a3d224b9-8dd7-4ecd-838b-ea908cb7530b
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HGVS expressions

NC_012920.1:m.10134C>A
J01415.2:m.10134C>A
ENST00000361227.2:c.76C>A

Uncertain Significance

Met criteria codes 2

PM2_Supporting PP4

Not Met criteria codes 5

BP4 PS3 PS4 PP1 PP3

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.10134C>A (p.Q26K) variant in MT-ND3 has been reported in one individual to date, in a girl with Leigh syndrome spectrum disorder (PMID: 25118196). She was reportedly slower than her siblings in reaching motor milestones and at 4-years-old lost the ability to jump, developed an abnormal gait, and had speech difficulty. At 4.5-years-old, she developed worsening speech, mobility, balance, and behaviors after undergoing anesthesia. Brain MRI performed at this time showed extensive signal abnormality involving putamen, globus pallidus bilaterally, and the cerebral peduncles, and brain MRS showed elevated lactate in the basal ganglia. Blood and cerebrospinal fluid (CSF) lactates were normal. Muscle biopsy showed fat accumulation and slightly increased subsarcolemmal mitochondrial aggregates. Liver biopsy showed increased glycogen content and mild biliary ductular proliferation, and electron microscopy showed occasional moderately enlarged mitochondria with paracrystalline and crystalline inclusions. The variant was present at homoplasmy in blood, fibroblasts, liver, and muscle. As this is the only case reported to date, PS4 could not be applied. Complex I deficiency was noted in muscle, and exome sequencing was performed in the proband, her parents, and three healthy siblings ruling out other known genetic etiologies (PMID:

25118196; PP4). This variant segregated with disease features in this family as her healthy mother had the variant present 1% in blood, however this does not meet criteria to apply PP1_supporting (at least two segregations). The computational predictor APOGEE gives a consensus rating of neutral with a score of 0.19 (Min=0, Max=1), which predicts no damaging effect on gene function, however an updated version of this predictor (APOGEE2) predicts a deleterious effect with a score of 0.752. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). 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 November 28, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM2_supporting, PP4.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PP4	✔	Complex I deficiency was noted in muscle, and exome sequencing was performed in the proband, her parents, and three healthy siblings ruling out other known genetic etiologies (PMID: 25118196; PP4).

Not Met criteria codes

BP4	✖	The computational predictor APOGEE gives a consensus rating of neutral with a score of 0.19 (Min=0, Max=1), which predicts no damaging effect on gene function, however an updated version of this predictor (APOGEE2) predicts a deleterious effect with a score of 0.752.
PS3	✖	There are no cybrids, single fiber studies, or other functional assays reported on this variant.
PS4	✖	The m.10134C>A (p.Q26K) variant in MT-ND3 has been reported in one individual to date, in a girl with Leigh syndrome spectrum disorder (PMID: 25118196). She was reportedly slower than her siblings in reaching motor milestones and at 4-years-old lost the ability to jump, developed an abnormal gait, and had speech difficulty. At 4.5-years-old, she developed worsening speech, mobility, balance, and behaviors after undergoing anesthesia. Brain MRI performed at this time showed extensive signal abnormality involving putamen, globus pallidus bilaterally, and the cerebral peduncles, and brain MRS showed elevated lactate in the basal ganglia. Blood and cerebrospinal fluid (CSF) lactates were normal. Muscle biopsy showed fat accumulation and slightly increased subsarcolemmal mitochondrial aggregates. Liver biopsy showed increased glycogen content and mild biliary ductular proliferation, and electron microscopy showed occasional moderately enlarged mitochondria with paracrystalline and crystalline inclusions. The variant was present at homoplasmy in blood, fibroblasts, liver, and muscle. As this is the only case reported to date, PS4 could not be applied.
PP1	✖	This variant segregated with disease features in this family as her healthy mother had the variant present 1% in blood, however this does not meet criteria to apply PP1_supporting (at least two segregations).
PP3	✖	The computational predictor APOGEE gives a consensus rating of neutral with a score of 0.19 (Min=0, Max=1), which predicts no damaging effect on gene function, however an updated version of this predictor (APOGEE2) predicts a deleterious effect with a score of 0.752.

Curation History

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