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Variant: m.10197G>A

Version: 1.1

CA120640

9715 (ClinVar)

Gene: MT-ND3 (HGNC:4537)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: c72f6ab6-c819-4a12-9d85-fe7e9d5cbc57
Approved on: 2022/7/25
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HGVS expressions

NC_012920.1:m.10197G>A
J01415.2:m.10197G>A
ENST00000361227.2:c.139G>A

Pathogenic

Met criteria codes 6

PS4 PM6 PP1_Moderate PM2_Supporting PS3_Supporting 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.10197G>A (p.A47T) variant in MT-ND3 has been reported in at least 22 probands with primary mitochondrial disease. Affected individuals had variable ages of onset (first months of life to childhood to adulthood). Features included Leigh syndrome, Leigh syndrome/MELAS overlap, and LHON with good visual recovery. Heteroplasmy levels were variable among tissues and affected individuals, and ranged from 10% (in an individual with LHON) to homoplasmy (in an individual with Leigh syndrome; PS4; PMIDs: 15372108, 17152068, 17413873, 18977334, 19458970, 20818383, 20972245, 24708134, 30128709, 30199507, 30776730, 32045392; two articles with no PMIDs: Pereira et al., 2019; JIEMS, 2019, Vol7: e20180003; Huang et al., 2017, J Clin Exp Ophthalmol 2017, 8:4). This variant segregated with disease in multiple affected members in multiple families and several healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 17152068, 17413873, 30128709, 30776730). This variant occurred de novo in at least three individuals (PM6_moderate, PMIDs: 24708134, 17413873; article with no PMID: Huang et al., 2017, J Clin Exp Ophthalmol 2017, 8:4). There are four occurrences of this variant in the GenBank dataset, and three of these four are not listed as patient sequences. However, upon discussion

on the Expert Panel (EP) call, concern was raised that phylogenetic studies use patient samples and submit these to GenBank. This variant is absent in gnomAD v3.1.2 and in Helix dataset so the EP agreed to consider this supporting line of evidence (PM2_supporting). Cybrid studies showed a correlation between higher heteroplasmy level and lower complex I activity (PS3_supporting, PMID: 17152068). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.88 (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_supporting, PM6_moderate, PS4.

Met criteria codes

PS4	✔	The m.10197G>A (p.A47T) variant in MT-ND3 has been reported in at least 22 probands with primary mitochondrial disease. Affected individuals had variable ages of onset (first months of life to childhood to adulthood). Features included Leigh syndrome, Leigh syndrome/MELAS overlap, and LHON with good visual recovery. Heteroplasmy levels were variable among tissues and affected individuals, and ranged from 10% (in an individual with LHON) to homoplasmy (in an individual with Leigh syndrome; PS4; PMIDs: 15372108, 17152068, 17413873, 18977334, 19458970, 20818383, 20972245, 24708134, 30128709, 30199507, 30776730, 32045392; two articles with no PMIDs: Pereira et al., 2019; JIEMS, 2019, Vol7: e20180003; Huang et al., 2017, J Clin Exp Ophthalmol 2017, 8:4).
PM6	✔	This variant occurred de novo in at least three individuals (PM6_moderate, PMIDs: 24708134, 17413873; article with no PMID: Huang et al., 2017, J Clin Exp Ophthalmol 2017, 8:4).
PP1_Moderate	✔	This variant segregated with disease in multiple affected members in multiple families and several healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 17152068, 17413873, 30128709, 30776730).
PM2_Supporting	✔	There are four occurrences of this variant in GenBank dataset, and three of these four are not listed as patient sequences. However, upon discussion on the Expert Panel (EP) call, concern was raised that phylogenetic studies use patient samples and submit these to GenBank. This variant is absent in gnomAD v3.1.2 and in Helix dataset so the EP agreed to consider this supporting line of evidence (PM2_supporting).
PS3_Supporting	✔	Cybrid studies showed a correlation between higher heteroplasmy level and lower complex I activity (PS3_supporting, PMID: 17152068).
PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.88 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3).

Curation History

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

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