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Variant: m.10191T>C

Version: 1.1

CA120637

9712 (ClinVar)

Gene: MT-TW (HGNC:4578)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: a760863d-1683-4dcf-a773-0807adc86d85
Approved on: 2022/8/23
Published on: 2022/9/2

HGVS expressions

NC_012920.1:m.10191T>C
J01415.2:m.10191T>C
ENST00000361227.2:c.133T>C

Pathogenic

Met criteria codes 5

PP3 PM6_Strong PS3_Supporting PM2_Supporting PS4

Not Met criteria codes 1

PP1

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.10191T>C (p.S45P) variant in MT-ND3 has been reported in at least 30 unrelated individuals with primary mitochondrial disease. Of note, to our knowledge, all reported individuals have been the only affected person in the family. Affected individuals had variable ages of onset (birth to 20s) and outcomes (death in first month of life to alive in 20s at the time of report). Features included Leigh syndrome, MELAS-like syndrome, and Leigh/MELAS overlap, as well as epilepsia partialis continua (EPC) and optic atrophy. Heteroplasmy levels ranged from 13%-100% in affected individuals (PS4; PMIDs: 11456298, 14684687, 15576045, 14705112, 16044424, 16023078, 17535832, 18078792, 19135620, 19617458, 19520270, 20691940, 20226758, 20972245, 22364517, 28429146, 27450679, 30128709, 31261379). There is one report of this variant segregating with disease features as a healthy mother of a proband had the variant present at 3% in blood (PMID: 11456298), however this does not meet criteria to apply PP1_supporting (at least two segregations). This variant was seen in the mother's blood in two other families (36% heteroplasmy in PMID: 16044424; 5% in mother's blood and undetectable in maternal grandmother's blood in PMID: 16023078), however no clinical details were provided on these family members to know if they were healthy

or affected. There are at least six reports of de novo occurrences of this variant (PM6_strong; PMIDs: 14705112, 18078792, 19520270, 22364517, 27450679). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Cybrid studies supported the functional impact of this variant (PS3_supporting; PMID: 14705112). 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 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 August 23, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM2_supporting, PP3, PS3_supporting, PM6_strong, PS4.

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).
PM6_Strong	✔	There are at least six reports of de novo occurrences of this variant (PM6_strong; PMIDs: 14705112, 18078792, 19520270, 22364517, 27450679).
PS3_Supporting	✔	Cybrid studies supported the functional impact of this variant (PS3_supporting; PMID: 14705112).
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PS4	✔	The m.10191T>C (p.S45P) variant in MT-ND3 has been reported in at least 30 unrelated individuals with primary mitochondrial disease. Of note, to our knowledge, all reported individuals have been the only affected person in the family. Affected individuals had variable ages of onset (birth to 20s) and outcomes (death in first month of life to alive in 20s at the time of report). Features included Leigh syndrome, MELAS-like syndrome, and Leigh/MELAS overlap, as well as epilepsia partialis continua (EPC) and optic atrophy. Heteroplasmy levels ranged from 13%-100% in affected individuals (PS4; PMIDs: 11456298, 14684687, 15576045, 14705112, 16044424, 16023078, 17535832, 18078792, 19135620, 19617458, 19520270, 20691940, 20226758, 20972245, 22364517, 28429146, 27450679, 30128709, 31261379).

Not Met criteria codes

PP1	✖	There is one report of this variant segregating with disease features as a healthy mother of a proband had the variant present at 3% in blood (PMID: 11456298), however this does not meet criteria to apply PP1_supporting (at least two segregations). This variant was seen in the mother's blood in two other families (36% heteroplasmy in PMID: 16044424; 5% in mother's blood and undetectable in maternal grandmother's blood in PMID: 16023078), however no clinical details were provided on these family members to know if they were healthy or affected.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.10191T>C	Pathogenic	Mitochondrial Disease	2022-09-02	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-TW
View	m.10191T>C	Pathogenic	Mitochondrial Disease	2022-09-02	1.0	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	N/A

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