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: m.10158T>C

Version: 1.1

CA120639

9714 (ClinVar)

Gene: MT-ND3 (HGNC:4537)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: a6286886-7f30-4c11-8ebb-5a936eb6f1c9
Approved on: 2021/10/26
Published on: 2021/10/26

HGVS expressions

NC_012920.1:m.10158T>C
J01415.2:m.10158T>C
ENST00000361227.2:c.100T>C

Pathogenic

Met criteria codes 6

PS4 PM2_Supporting PM6_Strong PP1 PP3 PS3_Supporting

Not Met criteria codes 12

BA1 BS1 BS4 BS3 BS2 BP5 BP7 BP2 PVS1 PS1 PM5 PM4

Evidence Links 1

Expert Panel

Mitochondrial Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The m.10158T>C (p.S34P) variant in MT-ND3 was reviewed by the Mitochondrial Disease Nuclear and Mitochondrial Variant Curation Expert Panel as part of the variant pilot for mitochondrial DNA variant specifications (McCormick et al., 2020; PMID: 32906214). This variant has been reported in >16 individuals with primary mitochondrial disease with onset ranging from the first year of life to adulthood and who had features variably consistent with Leigh syndrome, MELAS and MELAS-like, and/or lactic acidosis (PS4; PMID: 14705112; PMID: 14684687; PMID: 27348141; PMID: 28050007; PMID: 27742419; PMID: 28916229; PMID: 14764913; PMID: 22115768; PMID: 15576045; PMID: 30128709; PMID: 29237403; PMID: 31178082; https://doi.org/10.1111/ncn3.17). This variant has been identified as a de novo occurrence in at least seven probands with primary mitochondrial disease (PM6_strong; PMID: 28916229; PMID: 14764913; PMID: 14705112; PMID: 14684687; PMID: 31178082). This variant segregated with disease in multiple members in at least two families (PP1; PMID: 27742419; PMID: 14705112) and one healthy mother was found to have the variant at low heteroplasmy level (PMID: 14705112). This variant is absent from Mitomap's GenBank sequences and gnomAD v3.1.2 (PM2_Supporting). 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).

Cybrid studies showed tight correlation between variant heteroplasmy level and complex I activity (PS3_supporting; PMID: 14705112). 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 U24 Mitochondrial Disease Variant Curation Expert Panel as of August 20, 2020. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS3_supporting, PS4, PM2_supporting, PM6_strong, PP1, PP3).

Met criteria codes

PS4	✔	This variant has been reported in >16 individuals with primary mitochondrial disease with onset ranging from the first year of life to adulthood and who had features variably consistent with Leigh syndrome, MELAS and MELAS-like, and/or lactic acidosis (PS4; PMID: 14705112; PMID: 14684687; PMID: 27348141; PMID: 28050007; PMID: 27742419; PMID: 28916229; PMID: 14764913; PMID: 22115768; PMID: 15576045; PMID: 30128709; PMID: 29237403; PMID: 31178082; https://doi.org/10.1111/ncn3.17).
PM2_Supporting	✔	This variant is absent from Mitomap's GenBank sequences and gnomAD v3.1.2 (PM2_Supporting; query updated 3/22/2021).
PM6_Strong	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in at least 7 probands with primary mitochondrial disease (PM6_strong; PMID: 28916229; PMID: 14764913; PMID: 14705112; PMID: 14684687; PMID: 31178082). Per SVI de novo guidance Table 1 “phenotypic consistency” category of “phenotype consistent with gene but not highly specific” total is 3.5 points = strong
PP1	✔	This variant segregated with disease in multiple (three) members in at least two families, meeting specified criteria for PP1 [PP1; PMID: 27742419 (Grosso et al., 2017 - Healthy mother with lower heteroplasmy levels - 70% in urinary epithelium, 50% in buccal epithelium and 10% in lymphocytes) and PMID: 14705112 (McFarland et al., 2004 - Patient 3 (mother healthy and lower heteroplasmy (7% in FCL), sibling healthy and variant is undetectable)].
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).
PS3_Supporting	✔	Cybrid studies meeting criteria (showing tight correlation between % mutant and CI activity) Cybrid studies meeting criteria, however not reproduced so did not increase weight further PubMed:14705112

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	This is not a large mtDNA deletion
PS1	✖	No other nucleotide variant leading to same amino acid change reported at this site to be pathogenic (MITOMAP reports several other sequence variants in nt positions 10155-10161, however none are confirmed to be pathogenic and none lead to same amino acid change - query updated on 6/23/2020)
PM5	✖	No other amino acid change reported at this site to be pathogenic (MITOMAP reports several other sequence variants in nt positions 10155-10161, however none are confirmed to be pathogenic and none lead to same amino acid change - query updated on 6/23/2020)
PM4	✖	Not an insertion/deletion

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.10158T>C	Pathogenic	Mitochondrial Disease	2021-10-26	1.1	-	MT-ND3
View	m.10158T>C	Pathogenic	Mitochondrial Disease	2021-10-26	1.0	-	N/A

Showing 1 to 2 of 2 rows

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.

ClinGen Terms of Use.

¤ Powered by BCM's Genboree.