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:m.9191T>C

Version: 1.0

CA345914

40153 (ClinVar)

Gene: N/A
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 34880844-b4da-4064-a8c0-6a3e6a05ad7c
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HGVS expressions

NC_012920.1:m.9191T>C
J01415.2:m.9191T>C
ENST00000361899.2:c.665T>C

Likely Pathogenic

Met criteria codes 4

PP3 PM2_Supporting PS3_Supporting PM6_Supporting

Not Met criteria codes 4

PS1 PS4 PM5 PVS1

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.9191T>C (p.L222P) variant in MT-ATP6 has been reported once in the literature (PMID: 16217706, patient 2) in an individual with Leigh syndrome (94% heteroplasmy in muscle and 90% in fibroblasts; only testing done was MT-ATP6 and MT-ATP8 sequencing). This does not meet criteria for PS4_supporting which requires at least two unrelated affected individuals. This variant occurred de novo in this individual (absent in blood from mother and sister; PM6_supporting, PMID: 16217706). There are no large families reported in the literature to consider for evidence of segregation. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.75 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). Yeast model showed (1) failure to grow on glycerol (indicating at least an 80% reduction in ATP synthase activity/function), (2) 67-85% decrease in oxygen consumption, (3) <10% of control ATP synthesis, and (4) impaired ATPase assembly (PS3_supporting, PMID: 24316278). This variant meets criteria to be classified as uncertain significance however, after extensive discussion, this Expert Panel elected to modify the classification to likely pathogenic given consistent functional evidence of severe deleterious effect and rare nature of the variant, as well as being absent in healthy cohorts even at low heteroplasmy levels. In summary, this variant is classified as likely 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 January 10, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS3_supporting, PM2_supporting, PM6_supporting, PP3.

Met criteria codes

PP3	✔	In silico tools (APOGEE) predict this variant to be pathogenic with a score of 0.75 (PP3).
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Queried genbank, helix, gnomad 1/5/2022
PS3_Supporting	✔	Yeast model showed (1) failure to grow on glycerol (indicating at least an 80% reduction in ATP synthase activity/function), (2) 67-85% decrease in oxygen consumption, (3) <10% of control ATP synthesis, and (4) impaired ATPase assembly (PS3_supporting, PMID: 24316278). Yeast model showed (1) failure to grow on glycerol (indicating at least an 80% reduction in ATP synthase activity/function), (2) 67-85% decrease in oxygen consumption, (3) <10% of control ATP synthesis, and (4) impaired ATPase assembly (PS4_suppprting, PMID: 24316278) PubMed:24316278
PM6_Supporting	✔	This variant has been identified as a de novo occurrence in one individual with features consistent with primary mitochondrial disease (PM6_supporting, PMID: 16217706; per ClinGen de novo scoring guidance, scored 0.5 points for being absent in blood from mother and sister).

Not Met criteria codes

PS1	✖	No other nucleotide changes resulting in this amino acid change have been reported.
PS4	✖	This variant has been reported only once in the literature (PMID: 16217706, patient 2) in an individual with Leigh syndrome (94% heteroplasmy in muscle and 90% in fibroblasts; only testing done was MT-ATP6 and MT-ATP8 sequencing). This does not meet criteria for PS4_supporting which requires at least two unrelated affected individuals.
PM5	✖	No other amino acid changes at this position have been reported.
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 2 of 2 rows