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.8969G>A

Version: 1.1

CA199769

191364 (ClinVar)

Gene: MT-ATP6 (HGNC:4508)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: d577fcd6-dcef-47c4-9f9f-69c138f748a4
Approved on: 2022-06-30
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HGVS expressions

NC_012920.1:m.8969G>A
J01415.2:m.8969G>A
ENST00000361899.2:c.443G>A

Likely Pathogenic

Met criteria codes 6

PP1_Moderate PP3 PS4_Moderate PS2_Moderate PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PP4 PM6

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.8969G>A (p.S148N) variant in MT-ATP6 has been reported in at least five individuals from four families in the literature with features including nephrotic syndrome, developmental delay, seizures, stroke-like episodes, muscle weakness, brain atrophy, agenesis of the corpus callosum, hearing loss, Wolff-Parkinson-White syndrome, increased fasting level of glucose, liver steatosis, and failure to thrive, with heteroplasmy levels ranging from 61-96% (PS4_moderate; PMIDs: 25037980, 29350304, 27812026, 27450679). Additionally, this expert panel knew of two local families with affected individuals with this variant that the expert panel agreed to include. The variant was de novo in two of the four families reported in the literature (PS2_moderate; PMIDs: 25037980, 27450679). This variant segregated with disease in multiple affected members in one family and several healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 29350304). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Studies in cybrids and yeast support the functional impact of this variant (PS3_supporting; PMID: 27812026). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.57 (Min=0, Max=1), which predicts a damaging effect on gene function

(PP3). In summary, this variant meets criteria to be 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 March 28, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_moderate, PS2_moderate, PP1_moderate, PM2_supporting, PS3_supporting, PP3.

Met criteria codes

PP1_Moderate	✔	This variant segregated with disease in multiple affected members in one family and several healthy family members had lower to undetectable levels of the variant (PP1_moderate; PMIDs: 29350304).
PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.57 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3)
PS4_Moderate	✔	The m.8969G>A (p.S148N) variant in MT-ATP6 has been reported in at least five individuals from four families in the literature with features including nephrotic syndrome, developmental delay, seizures, stroke-like episodes, muscle weakness, brain atrophy, agenesis of the corpus callosum, hearing loss, Wolff-Parkinson-White syndrome, increased fasting level of glucose, liver steatosis, and failure to thrive, with heteroplasmy levels ranging from 61-96% (PS4_moderate; PMIDs: 25037980, 29350304, 27812026, 27450679). Additionally, this expert panel knew of two local families with affected individuals with this variant that the expert panel agreed to include.
PS2_Moderate	✔	The variant was de novo in two of the four families reported in the literature (PS2_moderate; PMIDs: 25037980, 27450679).
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Homoplasmic AF is is 0.0000% in Mitomap (0/54594), gnomAD (0/56434), and Helix (0/195983)
PS3_Supporting	✔	Studies in cybrids and yeast support the functional impact of this variant (PS3_supporting; PMID: 27812026). Cybrids showed defect transferred (98% mutant cybrid had ~70% reduction of basal respiration in OSR, >50% reduction in OCR); yeast model showed homoplasmic yeast had virtually no growth.) Wen et al PMID 27812026

Not Met criteria codes

PP4	✖	Respiratory chain enzyme analysis showed normal enzyme activities with decreased ATP production [Ishoanni 29350304] In another patient, "activities of complex I, III, and IV were normal as would be expected with a defect on complex V. However, the severe respiratory phenotype observed in skin fibroblast cell studies reflects the defect in complex V.and may explain why his clinical phenotype is so severe." [Burrage 25037980]
PM6	✖	Sallevelt et al 2017: 1 patient had mutant (95%) in blood, fibroblasts & muscle; mutation was not detected in the mother’s blood & urine (detection level <1%) Amniocentesis of sibling showed no mutant and the subsequent child was born healthy. (1/2 pt) Entire proband genome sequenced; unclear if mother was fully sequenced or had targeted sequencing.

Curation History

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