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.8993T>G

Version: 1.0

CA250380

9641 (ClinVar)

Gene: MT-ATP6 (HGNC:undefined)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 6cf1495e-53ff-4949-b2aa-ec1f11f3f24a
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HGVS expressions

NC_012920.1:m.8993T>G
J01415.2:m.8993T>G
ENST00000361899.2:c.467T>G

Pathogenic

Met criteria codes 7

PS4 PM6_Strong PP3 PM2_Supporting PM5 PP1_Moderate PS3_Supporting

Not Met criteria codes 4

BP4 PP4 BA1 BS1

Evidence Links 0

Expert Panel

Mitochondrial Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The m.8993T>G (p.L156R) variant in MT-ATP6 has been reported in >16 individuals with primary mitochondrial disease (PS4; PMIDs: 2137962, 8250532, 8240109, 7605802, 8505474, 9221962, 10208283, 16525806, 10660580). There are several reports of de novo occurrences of this variant (PM6_strong, PMIDs: 29602698, 27450679, 12134275). This variant is located at the same amino acid position as another well-known pathogenic variant, m.8993T>C (p.L156P) (PM5). 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: 2137962, 1436530, 1550128, 8095070, 9221962). This variant is absent in population databases after removing known patients with mitochondrial disease (PM2_supporting). In silico tools (APOGEE) predict this variant to be pathogenic (PP3). Cybrid studies supported the functional impact of this variant (PS3_supporting; PMID: 14998933, 8078883, 19875463). 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 on March 22, 2021. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS3_supporting, PS4, PM2_supporting, PM5, PM6_strong, PP1_moderate, PP3).

Met criteria codes

PS4	✔	Variant is present in ≥16 unrelated probands.
PM6_Strong	✔	5 counts assumed de novo - 0.5 points per case = 2.5 = strong (1 case in Uittenbogaard et al., 2018 - PMID: 29602698; 3 cases in Sallevelt et al., 2017 - PMID: 27450679; 1 case in Playan et al., 2002 - PMID: 12134275).
PP3	✔	APOGEE consensus is P at 0.95 [>0.5]
PM2_Supporting	✔	Total AF in Mitomap is 0.012% (6/51673) BUT ALL SIX ARE PATIENTS (2) or cybrids (4) with the mutation. Zero are controls. Absent in gnomADv3.1 gnomAD.v3.1 (0 /56368 mt sequences): Karczewski et al. 2020 PMID:32461654 Absent or <0.002% in Helix (0 homoplasmic + 1 heteroplasmic (0% hom., 0.0005% het.) /195983 mt sequences)
PM5	✔	m.8993T>C is also pathogenic at this codon. Fujii et al. P PMID: 9568930.
PP1_Moderate	✔	Families found with varying levels of the mutant heteroplasmy correlating roughly with the severity of disease (Holt et al., 1990 - PMID: 2137962; Shoffner et al., 1992 - PMID: 1436530; Tatuch et al., 1992 - PMID: 1550128; Ciafaloni et al., 1993 - PMID: 8095070; Uziel et al., 1997 - PMID: 9221962).
PS3_Supporting	✔	Functional validation in cybrid studies (Trounce et al., 1994 - PMID: 8078883; Manfredi et al., 2002 - PMID: 11925565; Mattiazzi et al., 2004 - PMID: 14998933; D'Aurelio et al., 2010 - PMID: 19875463).

Not Met criteria codes

BP4	✖	The APOGEE in-silico consensus score for pathogenicity is extremely high (0.95). To be a neutral variant, the score must be ≤ 0.5.
PP4	✖	Decreased ATP production and significantly reduced complex V activity in multiple patients. Parfait B et al. 1999 PMID:9950309; Morava et al. 2006 PMID: 16532470. However, to apply this criterion all other etiologies of CV deficiency would have to have been excluded which was not the case.
BA1	✖	AF in Mitomap is <5%. Not a haplogroup marker.
BS1	✖	AF in Mitomap is<0.5%.

Curation History

Showing 1 to 1 of 1 rows

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