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>C

Version: 1.0

CA120596

9642 (ClinVar)

Gene: MT-ATP6 (HGNC:undefined)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 78912cb6-b192-4466-9395-e4e013a9ef90
Approved on: 2021-05-05
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HGVS expressions

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

Pathogenic

Met criteria codes 5

PS3_Supporting PP3 PP1_Moderate PS4 PM5

Not Met criteria codes 4

PVS1 PM6 PS1 PS2

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.8993T>C (p.L156P) variant in MT-ATP6 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 and neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP) (PS4; PMIDs: 8395787, 16532470, 30128709, 29101127, 28003964, 26265210, 22819295, 19046652, 18055910, 16049925, 10604142). Per our literature review and a recently published review, there are no published de novo occurrences of this variant (PMID: 30763462). This variant is located at the same amino acid position as another well-known pathogenic variant, m.8993T>G (p.L156R) (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; PMID: 10604142). In silico tools predict this variant to be pathogenic (PP3). Cybrid studies (homoplasmic for this variant) showed reduced ATP production compared to Rho+ control cell lines (PS3_supporting; PMID: 19160410). In summary, this variant meets criteria to be classified as pathogenic for primary mitochondrial disease inherited in a maternal manner. This classification was approved by the NICHD U24 Mitochondrial Disease Variant

Curation Expert Panel on February 17, 2021. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS3_supporting, PS4, PM5, PP1_moderate, PP3).

Met criteria codes

PS3_Supporting	✔	See Figure 2 PubMed:19160410
PP3	✔	APOGEE: 0.95 (P) [also HmtVAR: 0.9 (P)]
PP1_Moderate	✔	More than 5 segregations - White et al., 1999: Family 11 (I-2 is healthy with 53% het in blood; II-2 is healthy with 74% het in blood; III-1 is healthy with 88% het in blood; III-3 is healthy with 17% het in blood; III-4 is healthy with 44% het in blood; and III-5 is healthy with 0% het in blood; PROBAND (III-2) is affected with 90% het in blood and 96% het in FCL); Family 12 (I-2 is healthy with 0% het in blood; II-2 is healthy with 77% het in blood; II-3 is healthy with 0% het in blood; II-4 is healthy with 0% het in blood; III-2 is healthy with 33% het in blood; PROBAND (III-1) is affected with 85% het in blood and 92% het in FCL); Family 13 (I-2 is healthy with 0% het in blood and 14% het in lymphoblasts; II-2 is healthy with 62% het in blood and 74% het in lymphoblasts; III-2 is affected with 89% het in blood, 93% het in FCL, 92% het in lymphoblasts, and 935 het in skeletal muscle; III-3 is affected with 83% het in blood and 76% het in lymphoblasts; PROBAND (III-1) is most severely affected family member with 93% het in blood, 92% het in FCL, 94% het in lymphoblasts, and 95% het in skeletal muscle).
PS4	✔	Variant present in ≥16 unrelated probands all meeting criteria outlined in mito VCEP specifications
PM5	✔	m.8993T>G (p.L156R) is a well-characterized pathogenic variant

Not Met criteria codes

PVS1	✖	This is a single nucleotide change.
PM6	✖	Per our review and Ganetzky et al., 2019, no de novo occurrences of m.8993T>C.
PS1	✖	No other pathogenic variants resulting in this amino acid change have been reported to date.
PS2	✖	Per our review and Ganetzky et al., 2019, no de novo occurrences of m.8993T>C.

Curation History

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