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Variant: NC_012920.1(MT-CO1):m.6951G>A

Version: 1.1

CA414790267

692687 (ClinVar)

Gene: MT-CO1 (HGNC:4512)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: b4c0f237-0696-452d-9341-565d9870a703
Approved on: 2023-07-10
Published on: 2023-08-03

HGVS expressions

NC_012920.1:m.6951G>A
J01415.2:m.6951G>A
ENST00000361624.2:c.1048G>A

Likely Benign

Met criteria codes 2

BP5 BP4

Not Met criteria codes 8

PS2 PS3 PS4 BA1 PP1 PM6 PM2 BS1

Evidence Links 2

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.6951G>A variant in MT-CO1 was reviewed by the Mitochondrial Disease Nuclear and Mitochondrial Variant Curation Expert Panel on July 10, 2023. There are no individuals or families with primary mitochondrial disease with this variant reported in the medical literature to our knowledge. Multiple unaffected family members were found to be homoplasmic for this variant in private databases known to this expert panel. In all of these families, the affected individuals had alternate genetic causes determined for their disease (BP5). This variant is present at low frequency in population databases. The frequency in gnomAD v3.1.2 is 26/56,416 (0.046%) with 26 homoplasmic occurrences and one heteroplasmic occurrence spread over eight top level haplogroups (single letter) with European, Asian, and African ancestry. The frequency in MITOMAP GenBank sequences is 20/59,389 (0.034%) spread over eight top level haplogroups with European, and Asian ancestry. The frequency in the Helix dataset is 75/195,983 (0.038%, all homoplasmic) plus an additional 13 heteroplasmic occurrences, all spread over 17 top level haplogroups with European, Asian, and African ancestry. Therefore, the frequency of this variant meets neither criteria for pathogenicity (<0.002%) nor benign status (>0.5%). The computational predictor APOGEE gives scores of 0.41

(“neutral”) in APOGEE1 and 0.101 (“likely benign”) in APOGEE2 (Min=0, Max=1), which predict a no impact on gene function (BP4). There are no cybrids, single fiber studies, or other functional assays reported on this variant to date. In summary, this variant meets criteria to be classified as likely benign for primary mitochondrial disease inherited in a mitochondrial manner. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on July 10, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied: BP4, BP5.

Met criteria codes

BP5	✔	Multiple unaffected family members were found to be homoplasmic for this variant in private databases known to this expert panel. In all of these families, the affected individuals had alternate genetic causes determined for their disease (BP5).
BP4	✔	This variant has raw scores in both APOGEE1 (0.41) and APOGEE2 (0.0499) of <0.5, which meets the criteria for a neutral or benign impact.

Not Met criteria codes

PS2	✖	There are no individuals or families with primary mitochondrial disease with this variant reported in the medical literature to our knowledge.
PS3	✖	There are no cybrids, single fiber studies, or other functional assays reported on this variant to date.
PS4	✖	There are no individuals or families with primary mitochondrial disease with this variant reported in the medical literature to our knowledge. There are two reports in ClinVar: one submittal for an individual reportedly with Leigh Disease, asserted as “Likely Benign”, and another submittal with no clinical condition provided. We do not count undocumented ClinVar reports for curation.
BA1	✖	This variant is present at low frequency in population databases. The frequency in gnomAD v3.1.2 is 26/56,416 (0.046%) with 26 homoplasmic occurrences and one heteroplasmic occurrence spread over eight top level haplogroups (single letter) with European, Asian, and African ancestry. The frequency in MITOMAP GenBank sequences is 20/59,389 (0.034%) spread over eight top level haplogroups with European, and Asian ancestry. The frequency in the Helix dataset is 75/195,983 (0.038%, all homoplasmic) plus an additional 13 heteroplasmic occurrences, all spread over 17 top level haplogroups with European, Asian, and African ancestry. Therefore, the frequency of this variant meets neither criteria for pathogenicity (<0.002%) nor benign status (>0.5%). m.6951G>A was reported in one individual in Haplogroup H in figure 3 of this paper. PubMed:16404693 m.6951G>A is a subclade marker in Phylotree: in small hg H4a1a4b2 in Phylotree.org (Phylotree 17) and in hg C4a1a* Phylotree 17 - Forensic Update 1.2 (this publication) PubMed:34072215
PP1	✖	There are no individuals or families with primary mitochondrial disease with this variant reported in the medical literature to our knowledge.
PM6	✖	There are no individuals or families with primary mitochondrial disease with this variant reported in the medical literature to our knowledge.
PM2	✖	

This variant is present at low frequency in population databases. The frequency in gnomAD v3.1.2 is 26/56,416 (0.046%) with 26 homoplasmic occurrences and one heteroplasmic occurrence spread over eight top level haplogroups (single letter) with European, Asian, and African ancestry. The frequency in MITOMAP GenBank sequences is 20/59,389 (0.034%) spread over eight top level haplogroups with European, and Asian ancestry. The frequency in the Helix dataset is 75/195,983 (0.038%, all homoplasmic) plus an additional 13 heteroplasmic occurrences, all spread over 17 top level haplogroups with European, Asian, and African ancestry. Therefore, the frequency of this variant meets neither criteria for pathogenicity (<0.002%) nor benign status (>0.5%).

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BS1

Population frequencies for this variant do not reach the criteria to meet BS1 (>0.5%) in either Mitomap, gnomAD, or Helix. Mitomap has 20/59,389 sequences (0.034%) spread over 7 haplogroups with European and Asian ancestry; gnomAD has 26/56,416 (0.046%) spread over 8 haplogroups with European, Asian, and African ancestry; Helix has 75/195,983 seq (0.038%), spread over 17 haplogroups with European, Asian, and African ancestry. The variant is seen in the updated Phylotree 17.1.2 as a marker for two very minor sub-clades, H4a1a4b2 and C4a1a* .

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Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NC_012920.1(MT-CO1):m.6951G>A	Likely Benign	Mitochondrial Disease	2023-08-03	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-CO1
View	NC_012920.1(MT-CO1):m.6951G>A	Likely Benign	Mitochondrial Disease	2023-08-03	1.0	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	N/A

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