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: m.3697G>A

Version: 1.1

CA120647

9733 (ClinVar)

Gene: MT-ND1 (HGNC:4535)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 92937acb-7e51-46ae-82f7-7a511b084dab
Approved on: 2022/3/24
Published on: 2022/3/24

HGVS expressions

NC_012920.1:m.3697G>A
J01415.2:m.3697G>A
ENST00000361390.2:c.391G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS3_Supporting PS4_Moderate PP1_Moderate

Not Met criteria codes 7

PM6 PM5 PM4 PVS1 BP4 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.3697G>A (p.G131S) variant in MT-ND1 has been reported in at least 14 individuals with primary mitochondrial disease from 8 families. Affected individuals had onset ranging from the first week of life to adulthood; and with features variably consistent with Leigh syndrome, MELAS, and LHON (PS4_moderate; PMIDs: 31996177, 30623604, 28429146, 24830958, 18977334, 17562939, 15466014). There are no reports of de novo occurrence of this variant. 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: 24830958, 17562939, 16969869, 15466014). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Functional studies supported the deleterious impact of this variant (PS3_supporting; PMID: 15466014). 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 22, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS3_supporting, PS4_moderate, PM2_supporting, PP1_moderate.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the GenBank data set, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PS3_Supporting	✔	Functional studies supported the deleterious impact of this variant. The patient fibroblast cell line had complex I deficiency, hybrid cells (patient cells fused with rho0 cells) did not restore complex I activity although when fused with cells from an individual with an nDNA etiology, complex I activity was restored. Tentative PubMed:15466014
PS4_Moderate	✔	The m.3697G>A (p.G131S) variant in MT-ND1 has been reported in 7 individuals with primary mitochondrial disease with onset ranging from the first week of life to adulthood; and who had features variably consistent with Leigh syndrome, MELAS, and LHON (PS4_moderate; PMIDs: 31996177, 30623604, 28429146, 24830958, 18977334, 17562939, 15466014).
PP1_Moderate	✔	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: 24830958, 17562939, 16969869, 15466014).

Not Met criteria codes

PM6	✖	Per our literature review, there are no reported de novo occurrences of this variant.
PM5	✖	There are no other pathogenic variants at this amino acid.
PM4	✖	This variant does not result in a protein length change.
PVS1	✖	This is not a deletion, nonsense, or frameshift variant.
BP4	✖	In silico tools (APOGEE) predict this variant to be neutral (0.36; BP4).
PS1	✖	There are no other pathogenic variants at this amino acid.
PS2	✖	Per our literature review, there are no reported de novo occurrences of this variant.

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.3697G>A	Likely Pathogenic	Mitochondrial Disease	2022-03-24	1.1	-	MT-ND1
View	m.3697G>A	Likely Pathogenic	Mitochondrial Disease	2022-03-24	1.0	-	N/A

Showing 1 to 2 of 2 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.

¤ Powered by BCM's Genboree.