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.7443A>G

Version: 1.1

CA347798

40158 (ClinVar)

Gene: MT-CO1 (HGNC:4512)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 90cab362-378c-4d46-b6d3-5ad3760fc316
Approved on: 2024-07-08
Published on: 2024-12-09

HGVS expressions

NC_012920.1:m.7443A>G
J01415.2:m.7443A>G
ENST00000361624.2:c.1540A>G

Uncertain Significance

Met criteria codes 2

PS3_Supporting PM2_Supporting

Not Met criteria codes 2

PS4 PP3

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.7443A>G (p.*514G) variant in MT-CO1 has been reported in one individual with primary mitochondrial disease to date (PMID: 10577941), in a child enrolled at the School for Deaf and Blind in Mongolia. He was reported to have been deaf since infancy. The variant appeared to be homoplasmic. Information was not provided on the family history of this individual. There are no additional case reports to our knowledge. There are several occurrences of this variant in population databases (Mitomap: 1/61,134, gnomAD: 1/56,434, Helix: 4/195,893). Although there are several occurrences, the frequency is still low (PM2_supporting). There are no in-silico prediction tools for a stop-loss variant in mitochondrial DNA, although this variant would not be expected to cause run-through due to the excision of the tRNA immediately adjacent. Functional studies showed inefficient processing (29% of wild type) by tRNAseZ in the presence of this variant (PS3_supporting; PMID: 16361254). In summary, this variant meets criteria to be classified as uncertain significance 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 8, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS3_supporting, PM2_supporting.

Met criteria codes

PS3_Supporting	✔	Yan et al 2006 (PMID 16361254) demonstrated inefficient processing (29% of WT) by tRNAseZ in the presence of this mutation.
PM2_Supporting	✔	There are several occurrences in population databases (Mitomap: 1/61,134, gnomAD: 1/56,434, Helix: 4/195,893). Although there are several occurrences, the frequency is still low (PM2_supporting).

Not Met criteria codes

PS4	✖	The MT-CO1 m.7443A>G (*514G) variant was reported in one student of ~400 from the School for Deaf and Blind in Mongolia. He was reported to have been deaf since infancy (Pandya et al 1999, PMID 10577941). The variant appeared to be homoplasmic by Sequenase PCR sequencing. Both m.1555A>G and m.7445A>G were absent. No family information was reported for this patient and no other mitochondrial disease cases were found with m.7443A>G in our review of the literature.
PP3	✖	There are no in-silico prediction tools for a stop-loss variant in mitochondrial DNA, although this variant would not be expected to cause run-through due to the excision of the tRNA immediately adjacent.

Curation History

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