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.7471dup

Version: 1.1

CA214937

42226 (ClinVar)

Gene: MT-TS1 (HGNC:4574)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 70c69556-61de-4e88-8de9-ae8b0bcba308
Approved on: 2022/11/14
Published on: 2023/1/5

HGVS expressions

NC_012920.1:m.7471dup
J01415.2:m.7471dup

Pathogenic

Met criteria codes 3

PS3_Supporting PP1_Moderate PS4

Not Met criteria codes 4

PP3 PM6 PM2 PS2

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.7471dup variant in MT-TS1 has been reported in >16 unrelated individuals with primary mitochondrial disease across several haplogroups. This variant is most commonly associated with sensorineural hearing loss however affected individuals can also have other features. Affected individuals have been reported with features including MELAS, cerebellar ataxia, myoclonus, epilepsy, white matter disease, intellectual disability, cerebellar atrophy, exercise intolerance, and hypotonia; and this variant has been seen in affected individuals in the homoplasmic and heteroplasmic states (PS4; PMIDs: 7581383, 9708714, 9832034, 9778262, 9778273, 10094190, 15482956, 11378827, 15292920, 15482956, 11378827, 15292920, 1533431, 16368237, 17637808, 15833431, 16368237). 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: 7581383, 9708714). Cybrid studies supported the functional impact of this variant (PS3_supporting; PMID: 10545608). There are no de novo occurrences to our knowledge. There are no in silico predictors for this type of variant in mitochondrial DNA. In summary, this variant meets criteria to be classified as likely pathogenic however this Expert Panel elected to modify the classification to pathogenic given the overwhelming evidence of pathogenicity. Furthermore, the mitochondrial DNA variant specifications are known to not be optimized for pathogenic variants that tend to be homoplasmic in nature, have reduced penetrance, and/or variants that are insertions. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease

Variant Curation Expert Panel on November 14, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied(PMID: 32906214): PS4, PP1_moderate, PS3_supporting.

Met criteria codes

PS3_Supporting	✔	Cybrid studies supported the functional impact of this variant (PS3_supporting; PMIDs: 10545608).
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: 7581383, 9708714).
PS4	✔	The m.7471dup variant in MT-TS1 has been reported in >16 unrelated individuals with primary mitochondrial disease and across several haplogroups. This variant is most commonly associated with sensorineural hearing loss however affected individuals can also have other features. Affected individuals have been reported with features including MELAS, cerebellar ataxia, myoclonus, epilepsy, white matter disease, ID, cerebellar atrophy, exercise intolerance, hypotonia; and this variant has been seen in affected individuals in the homoplasmic and heteroplasmic states (PS4; PMIDs: 7581383, 9708714, 9832034, 9778262, 9778273, 10094190, 15482956, 11378827, 15292920, 15482956, 11378827, 15292920, 1533431, 16368237, 17637808, 15833431, 16368237).

Not Met criteria codes

PP3	✖	There are no in silico predictors for this type of variant in mitochondrial DNA.
PM6	✖	There are no de novo occurrence to our knowledge.
PM2	✖	There are several occurrences in population databases, however some of these are from reported affected individuals. Heteroplasmic 26/56307 = 0.046%.
PS2	✖	There are no de novo occurrence to our knowledge.

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NC_012920.1:m.7471dup	Pathogenic	Mitochondrial Disease	2023-01-05	1.1	-	MT-TS1
View	NC_012920.1:m.7471dup	Pathogenic	Mitochondrial Disease	2023-01-05	1.0	-	N/A

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