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Variant: m.14459G>A

Version: 1.1

CA120625

9689 (ClinVar)

Gene: MT-ND6 (HGNC:4541)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: a87cdf9b-c0e4-4872-9a99-be710c312acc
Approved on: 2021/11/1
Published on: 2021/11/1

HGVS expressions

NC_012920.1:m.14459G>A
J01415.2:m.14459G>A
ENST00000361681.2:c.215C>T

Pathogenic

Met criteria codes 5

PP3 PM6 PP1_Moderate PS4 PS3_Supporting

Not Met criteria codes 1

PM5

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.14459G>A (p.A72V) variant in MT-ND6 was reviewed by the Mitochondrial Disease Nuclear and Mitochondrial Variant Curation Expert Panel as part of the variant pilot for mitochondrial DNA variant specifications (McCormick et al., 2020; PMID: 32906214). This variant has been reported in >16 individuals with primary mitochondrial disease with variable features ranging from Leber Hereditary Optic Neuropathy (LHON) with or without dystonia, Leigh syndrome, bilateral basal ganglia lesions, ataxia, and migraines (PS4; PMIDs: 8016139, 7654063, 16380132, 10894222, 14735584, 21749722, 14735585, 28503604, 32045392, 29408632, 22426787). This variant has been identified as a de novo occurrence in at least 2 probands with primary mitochondrial disease (PM6; PMIDs: 14735584, 10894222). This variant heteroplasmy level segregated with severity in six family members from four families (PP1_moderate; PMIDs: 22426787, 21749722, 7654063, 8016139). The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.93 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). Cybrid studies supported the functional impact of this variant including a deficiency seen in patient cell line that was transferred to cybrids with a high mutant load and study was reproducible (PS3_supporting; PMID: 8622678). In summary, this variant meets criteria to be classified as pathogenic for primary mitochondrial disease inherited in a mitochondrial manner. This classification was approved by the NICHD U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel as of August 20, 2020. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS4, PM6, PP1_moderate, PP3, PS3_supporting.

Met criteria codes

PP3	✔	The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.93 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3).
PM6	✔	This variant has been identified as a de novo occurrence in at least 2 probands with primary mitochondrial disease (PM6; PMIDs: 14735584, 10894222). Per SVI scoring guidance, each case is 0.5 point = 1 = moderate
PP1_Moderate	✔	This variant heteroplasmy level segregated with severity in six family members from four families (PP1_moderate; PMIDs: 22426787, 21749722, 7654063, 8016139).
PS4	✔	This variant has been reported in >16 individuals with primary mitochondrial disease with variable features ranging from Leber Hereditary Optic Neuropathy (LHON) with or without dystonia, Leigh syndrome, bilateral basal ganglia lesions, ataxia, and migraines (PS4; PMIDs: 8016139, 7654063, 16380132, 10894222, 14735584, 21749722, 14735585, 28503604, 32045392, 29408632, 22426787).
PS3_Supporting	✔	Cybrid studies supported the functional impact of this variant including a deficiency seen in patient cell line that was transferred to cybrids with a high mutant load and study was reproducible (PS3_supporting; PMID: 8622678).

Not Met criteria codes

PM5	✖	No other variants reported in this region

Curation History

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