Variant: m.12147G>A

Version: 1.1

CA120576

9610 (ClinVar)

Gene: MT-TH (HGNC:4564)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 76c21ebb-4a23-458c-a7d2-738c4df20b87
Approved on: 2023-01-09
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HGVS expressions

NC_012920.1:m.12147G>A
J01415.2:m.12147G>A

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PS4_Supporting PM6 PS3_Supporting

Not Met criteria codes 1

PS2

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.12147G>A variant in MT-TH has been reported in two unrelated probands with features of primary mitochondrial disease. Both individuals were males with symptom onset in late teens to early 20s, developed seizures, and had COX-negative fibers identified on muscle biopsy. One individual also had ragged red fibers, and complex I and IV deficiencies. Additional features seen include sensorineural hearing loss, optic atrophy, ptosis, migraines, ataxia, myoclonus, muscle weakness, hepatic failure consistent with Reye syndrome, lactic acidosis, and hyperCKemia. Heteroplasmy in the affected individuals ranged from 86% in muscle to undetectable in hair (PS4_supporting; PMIDs: 14967777, 15111688). This variant occurred de novo in one individual (absent in blood, urine, hair, and muscle from mother as well as two sisters, two maternal aunts, and two maternal uncles; PM6, PMID: 15111688). The computational predictor MitoTIP suggests this variant is pathogenic (93.5 percentile) and HmtVAR predicts it to be pathogenic score of 1 (PP3). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). Single fiber testing was performed in muscle fibers from both affected individuals, supporting the functional impact of this variant (PS3_supporting). In one individual, the mean heteroplasmy level in abnormal

fibers was 90% ± 2% (n=22) and in normal fibers was 58% ± 6% (n=15; P = 0.007). Furthermore, in ragged red fibers, the mean heteroplasmy level was 94% (PMID: 14967777). In the other individual, the mean heteroplasmy level in COX-deficient fibers was 94.6 ± 1.53% (n = 12) and in COX-positive fibers was 32.5 ± 6.18% (n = 10; p < 0.0001; PMID: 15111688). 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 ClinGen Mitochondrial Disease Variant Curation Expert Panel on January 9, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_supporting, PM6, PM2_supporting, PP3, PS3_supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic (93.5 percentile) and HmtVAR predicts it to be pathogenic score of 1 (PP3).
PS4_Supporting	✔	The m.12147G>A variant in MT-TH has been reported in two unrelated probands with features of primary mitochondrial disease. Both individuals were males with symptom onset in late teens to early 20s, developed seizures, and had COX-negative fibers identified on muscle biopsy. One individual also had ragged red fibers, and complex I and IV deficiencies. Additional features seen include sensorineural hearing loss, optic atrophy, ptosis, migraines, ataxia, myoclonus, muscle weakness, hepatic failure consistent with Reye syndrome, lactic acidosis, and hyperCKemia. Heteroplasmy in the affected individuals ranged from 86% in muscle to undetectable in hair (PS4_supporting; PMIDs: 14967777, 15111688).
PM6	✔	This variant occurred de novo in one individual (absent in blood, urine, hair, and muscle from mother as well as two sisters, two maternal aunts, and two maternal uncles; PM6, PMID: 15111688).
PS3_Supporting	✔	Single fiber testing was performed in muscle fibers from both affected individuals, supporting the functional impact of this variant (PS3_supporting). In one individual, the mean heteroplasmy level in abnormal fibers was 90% ± 2% (n=22) and in normal fibers was 58% ± 6% (n=15; P = 0.007). Furthermore, in ragged red fibers, the mean heteroplasmy level was 94% (PMID: 14967777). In the other individual, the mean heteroplasmy level in COX-deficient fibers was 94.6 ± 1.53% (n = 12) and in COX-positive fibers was 32.5 ± 6.18% (n = 10; p < 0.0001; PMID: 15111688). COX negative fibers (90%) than in COX positive fibers (58%), p= 0.007 PubMed:14967777 COX negative fibers (94.6%) than in COX positive fibers (32.5%), p < 0.0001 PubMed:15111688

Not Met criteria codes

PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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