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Variant: NC_012920.1:m.1661A>G

Version: 1.1

CA16040644

370043 (ClinVar)

Gene: MT-TV (HGNC:4577)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: ce750f8c-53f8-4d28-9bb8-5a0bef5a665b
Approved on: 2023-10-23
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HGVS expressions

NC_012920.1:m.1661A>G
J01415.2:m.1661A>G

Uncertain Significance

Met criteria codes 2

PS4_Supporting BP4

Not Met criteria codes 5

PM6 PM2 PS2 PS3 PP1

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.1661A>G variant in MT-TV has been reported in two unrelated families (PS4_supporting). Limited phenotypic details are provided in the first reported family (Patient 6 in Bacalhau et al., 2017, PMID: 28027978) however a subsequent publication reported the proband in this family had seizures, hypotonia, developmental delay, elevated blood lactate, and combined deficiency of electron transport chain enzyme activities (PMID: 32715519). The heteroplasmy level and information on family members and/or testing in family members were not reported in this first kindred. The second family reported was a large kindred from the Venezuelan Andes with axonal Charcot-Marie-Tooth (CMT) disease (motor and sensory neuropathy). Muscle weakness, muscle atrophy, and ataxia were also seen in the affected individuals in this family (Fay et al., 2020, PMID: 32715519). Muscle biopsies performed in several individuals showed denervation and reinnervation, in addition to mitochondrial hyperplasia, mildly increased glycogen, and the presence of mitochondrial crystalline arrays. Combined respiratory chain enzyme deficiencies were also seen in affected individuals from this kindred. The variant was present at homoplasmy in blood and/or muscle in both affected and unaffected individuals from this kindred. There are no reported de novo

occurrences on this variant to our knowledge. The computational predictor MitoTIP suggests this variant is benign (27.6 percentile; BP4).This variant is present in population databases (MITOMAP: 1/61,168 sequences, AF=0.002%, haplogroup (Hg) H1c; Helix: 2/195,983 (0.001%), also 19 heteroplasmic occurrences, homoplasmic occurrences in Hg I and V, heteroplasmic in multiple haplogroups; and gnomAD v3.1.2: 2/56,398 (0.004%), also three heteroplasmic occurrences (heteroplasmy levels: 10-20%; 20-30%; 90-100%), one in Hg T, one in H, one in B, one in K, one in L3). Given the frequency of this variant, it does not meet PM2 criterion. There are no cybrids, single fiber studies, or other functional assays reported on this variant. 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 October 23, 2023. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4_supporting, BP4

Met criteria codes

PS4_Supporting	✔	The m.1661A>G variant in MT-TV has been reported in two unrelated families (PS4_supporting). Limited phenotypic details are provided in the first reported family (Patient 6 in Bacalhau et al., 2017, PMID: 28027978) however a subsequent publication reported the proband in this family had seizures, hypotonia, developmental delay, elevated blood lactate, and combined deficiency of electron transport chain enzyme activities (PMID: 32715519). The heteroplasmy level and information on family members and/or testing in family members were not reported in this first kindred. The second family reported was a large kindred from the Venezuelan Andes with axonal Charcot-Marie-Tooth (CMT) disease (motor and sensory neuropathy). Muscle weakness, muscle atrophy, and ataxia were also seen in the affected individuals in this family (Fay et al., 2020, PMID: 32715519). Muscle biopsies performed in several individuals showed denervation and reinnervation, in addition to mitochondrial hyperplasia, mildly increased glycogen, and the presence of mitochondrial crystalline arrays. Combined respiratory chain enzyme deficiencies were also seen in affected individuals from this kindred. The variant was present at homoplasmy in blood and/or muscle in both affected and unaffected individuals from this kindred.
BP4	✔	The computational predictor MitoTIP suggests this variant is benign (27.6 percentile; BP4).

Not Met criteria codes

PM6	✖	There are no reported de novo occurrences on this variant to our knowledge.
PM2	✖	This variant is present in population databases (MITOMAP: 1/61,168 sequences, AF=0.002%, haplogroup (Hg) H1c; Helix: 2/195,983 (0.001%), also 19 heteroplasmic occurrences, homoplasmic occurrences in Hg I and V, heteroplasmic in multiple haplogroups; and gnomAD v3.1.2: 2/56,398 (0.004%), also three heteroplasmic occurrences (heteroplasmy levels: 10-20%; 20-30%; 90-100%), one in Hg T, one in H, one in B, one in K, one in L3). Given the frequency of this variant, it does not meet PM2 criterion.
PS2	✖	There are no reported de novo occurrences on this variant to our knowledge.
PS3	✖	There are no cybrids, single fiber studies, or other functional assays reported on this variant.
PP1	✖	No testing was mentioned in the first family reported and the variant was present at homoplasmy in affected and unaffected family members from the second family, precluding consideration for PP1.

Curation History

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