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Variant: NC_012920.1(MT-TK):m.8296A>G

Version: 1.1

CA120557

9584 (ClinVar)

Gene: MT-ATP6 (HGNC:4508)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 2723e9dc-d079-4e5c-98b7-07425e227416
Approved on: 2025/2/4
Published on: 2025/5/28

HGVS expressions

NC_012920.1:m.8296A>G
J01415.2:m.8296A>G

Uncertain Significance

Met criteria codes 1

PP3

Not Met criteria codes 6

PM6 PM2 PS2 PS3 PS4 PP1

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.8296A>G variant in MT-TK has been reported in 18 unrelated individuals with primary mitochondrial disease with varying phenotypes (diabetes, hypertrophic cardiomyopathy, optic atrophy, sensorineural hearing loss, and generalized epilepsy; 10 subjects reported in PMIDs: 9802769, 9571188, 10525672; additional subjects reported in PMIDs: 10737988, 12504210, 18651333, 20143911, 37573175), however analyses for other genetic etiologies were limited in these affected individuals precluding their inclusion in this curation. The variant was present in some affected individuals at homoplasmy and in others at heteroplasmy. In at least one family, the variant was present at homoplasmy in the proband and in his healthy mother and sister (PMID: 18651333). There are no reported de novo occurrences to our knowledge. This variant is present in population databases and is seen in individuals from several different haplogroups (MITOMAP: 0.061%, 38/61,883; gnomAD v3.1.2: 0.044%, 25/56,432 homoplasmic occurrences, one heteroplasmic occurrence; Helix: 0.048%, 94/195,893 homoplasmic occurrences). The computational predictor MitoTIP suggests this variant is pathogenic (72.3 percentile) and HmtVAR predicts it to be pathogenic score of 0.85 (PP3). Single fiber testing showed similar levels of the variant in COX-

negative ragged red fibers and normal fibers (PMID: 9932960), and cybrid studies showed no significant differences from wild type (PMID: 11857739). 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 February 4, 2025. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PP3.

Met criteria codes

PP3	✔	The computational predictor MitoTIP suggests this variant is pathogenic (72.3 percentile) and HmtVAR predicts it to be pathogenic score of 0.85 (PP3).

Not Met criteria codes

PM6	✖	There are no reported de novo occurrences to our knowledge.
PM2	✖	This variant is present in population databases and is seen in individuals from several different haplogroups (MITOMAP: 0.061%, 38/61,883; gnomAD v3.1.2: 0.044%, 25/56,432 homoplasmic occurrences, 1 heteroplasmic occurrence; Helix: 0.048%, 94/195,893 homoplasmic occurrences).
PS2	✖	There are no reported de novo occurrences to our knowledge.
PS3	✖	Single fiber testing showed similar levels of the variant in COX-negative ragged red fibers and normal fibers (PMID: 9932960), and cybrid studies showed no significant differences from wild type (PMID: 11857739). Protein synthesis and aminoacylation was similar to wild type. PubMed:11857739 COX-negative ragged red fibers (n = 5) had 99% ± 0.5 mutant mtDNA and normal fibers (n = 5) had 98.2% ± 1.3. PubMed:9932960
PS4	✖	The m.8296A>G variant in MT-TK has been reported in 18 unrelated individuals with primary mitochondrial disease with varying phenotypes (diabetes, hypertrophic cardiomyopathy, optic atrophy, sensorineural hearing loss, and generalized epilepsy; 10 subjects reported in PMIDs: 9802769, 9571188, 10525672; additional subjects reported in PMIDs: 10737988, 12504210, 18651333, 20143911, 37573175), however analyses for other genetic etiologies were limited in these affected individuals precluding their inclusion in this curation. The variant was present in some affected individuals at homoplasmy and in others at heteroplasmy.
PP1	✖	In at least one family, the variant was present at homoplasmy in the proband and in his healthy mother and sister (PMID: 18651333).

Curation History

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