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Variant: NC_012920.1:m.9205_9206del

Version: 1.2

CA120599

9646 (ClinVar)

Gene: MT-ATP6 (HGNC:4508)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: a29092c4-248c-4d4c-8b2b-e2145be5b4af
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HGVS expressions

NC_012920.1:m.9205_9206del
J01415.2:m.9205_9206del
ENST00000361899.2:c.679_680del

Likely Pathogenic

Met criteria codes 4

PS4_Supporting PM4 PM6_Supporting PM2_Supporting

Not Met criteria codes 4

PS2 PS3 PP1 PP4

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.9205_9206delTA (p.Ter227M) variant in MT-ATP6 has been reported in two unrelated probands with features of primary mitochondrial disease (neonatal lactic acidosis, failure to thrive, spasticity, microcephaly, developmental delay; PS4_supporting; PMIDs: 8739943, 15265003). The variant was de novo in one of these individuals (absent in mother and maternal grandmother's lymphocytes via PCR-SSCP; PM6_supporting; PMID: 8739943). In the other family, this variant segregated with disease in two unaffected family members as they had lower levels of the variant, however the unaffected mother's heteroplasmy level was still fairly high at >90% (PMID: 15265003). This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). There are no cybrids or single fiber studies reported on this variant. The loss residue removes the termination codon for MT-ATP6 and sets MT-CO3 immediately in frame. This results in decreased steady state level of RNA14, the ATPase 8- and 6-encoding bi-cistronic mRNA unit, causing dysregulation of mRNA stability (PM4, PMID: 12915481). This variant meets criteria to be classified as uncertain significance however, after extensive discussion, this Expert Panel elected to modify the classification to likely pathogenic given the functional evidence showing destabilization of the RNA.

In summary, this variant is classified as likely pathogenic for primary mitochondrial disease inherited in a mitochondrial manner. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM6_supporting, PM2_supporting, PM4, PS4_supporting.

Met criteria codes

PS4_Supporting	✔	This variant has been reported in two unrelated probands with features of primary mitochondrial disease (neonatal lactic acidosis, failure to thrive, spasticity, microcephaly, developmental delay; PS4_supporting; PMIDs: 8739943, 15265003).
PM4	✔	The loss residue removes the termination codon for MT-ATP6 and sets MT-CO3 immediately in frame. This results in decreased steady state level of RNA14, the ATPase 8- and 6-encoding bi-cistronic mRNA unit, causing dysregulation of mRNA stability (PM4, PMID: 12915481).
PM6_Supporting	✔	The variant was de novo in one of these individuals (absent in mother and maternal grandmother's lymphocytes via PCR-SSCP; PM6_supporting; PMID: 8739943).
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).

Not Met criteria codes

PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	There are no cybrids or single fiber studies reported on this variant. Western-blot analysis and in vitro synthesis results demonstrate that μΔRNA14 can still be translated despite the observation that all the 3'-termini of μΔRNA14 lacked a termination codon. The poly(A) extension would be predicted to be translated as polylysine. Although the natural length of the poly(A) extension is truncated in the μΔ transcripts, the short poly(A) would still be predicted to add several lysine residues to the C-terminus of ATPase 6, and it is not clear how the translating ribosome would disaggregate from the nascent polypeptide. Therefore it is possible that if the ATPase 6 is synthesized with this short extension that might not be identifiable by standard gel-electrophoresis techniques, the aberrant protein could affect normal assembly of the FoF1-ATP synthase, complex V (PMID: 14585098).
PP1	✖	In one family, this variant segregated with disease in two unaffected family members as they had lower levels of the variant, however the unaffected mother’s heteroplasmy level was still fairly high at >90% (PMID: 15265003).
PP4	✖	Biochemical evidence of decrease ATP synthase activity and COX deficiency however only the mitochondrial genome was sequenced (PMID:15265003).

Curation History

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