The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: m.6930G>A

Version: 1.1

CA120612

9668 (ClinVar)

Gene: MT-CO1 (HGNC:4512)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: f4dd39de-25f6-46fa-bb8c-b6677e5a2810
Approved on: 2024-01-22
Published on: 2024-03-14

HGVS expressions

NC_012920.1:m.6930G>A
J01415.2:m.6930G>A
ENST00000361624.2:c.1027G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PVS1_Strong PS3_Supporting PM6_Supporting

Not Met criteria codes 3

BP4 PS2 PP3

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.6930G>A (p.G343Ter) variant in MT-CO1 has been reported in one individual to date, in a woman with a multisystem disorder (PMID: 10441567). Clinical features included cataracts, profound sensorineural hearing loss, myoclonic epilepsy, cerebellar ataxia, progressive muscle weakness and atrophy, progressive vision loss due to optic atrophy, and a severe sensorimotor neuropathy. Brain imaging showed diffuse cerebellar atrophy and bilateral small symmetrical nodular hyperintensities in the basal ganglia (head of the caudatus and putamen). She had elevated blood lactate (5.8 mM, normal 0.1-2.2) and CK (1000 UI/L; normal <150). Muscle biopsy showed that only 10% of fibers showed normal COX staining and her complex IV activity was 10% of controls. The variant was present at 27% heteroplasmy in blood, 75% in muscle, and 33% in myoblasts. As this is the only case reported to date, PS4 could not be applied. The variant was absent in blood from her mother, sister, and four maternal aunts (PM6_supporting). Computational predictors are not applicable for this variant type precluding consideration for PP3 or BP4. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). This variant results in loss of the last 170 amino acids (33% of the protein, PVS1_strong). Cybrid studies supported the

functional impact of this variant (PS3_supporting; PMIDs: 10441567, 11595737). 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 22, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PM6_supporting, PM2_supporting, PS3_supporting, PVS1_strong.

Met criteria codes

PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PVS1_Strong	✔	This variant results in loss of the last 170 amino acids (33% of the protein, PVS1_strong).
PS3_Supporting	✔	Cybrid studies supported the functional impact of this variant (PS3_supporting; PMIDs: 10441567, 11595737).
PM6_Supporting	✔	The variant was absent in blood from her mother, sister, and four maternal aunts (PM6_supporting).

Not Met criteria codes

BP4	✖	Computational predictors are not applicable for this variant type precluding consideration for PP3 or BP4.
PS2	✖	The variant was absent in blood from her mother, sister, and four maternal aunts (PM6_supporting).
PP3	✖	Computational predictors are not applicable for this variant type precluding consideration for PP3 or BP4.

Curation History

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