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# *Variant: m.3733G>A*

Version: 1.1

*CA340950*

*9736 (ClinVar)*

**Gene**: MT-ND1 (HGNC:4535)
**Condition**: mitochondrial disease (MONDO:0044970)
**Inheritance Mode**: Mitochondrial inheritance
**UUID:** daa1d3fa-2de4-4e31-b8ad-af651dacd90e
**Approved on**: 2022-03-24
**Published on**: 2022-03-24

## *HGVS expressions*

**NC_012920.1:m.3733G>A**
J01415.2:m.3733G>A
ENST00000361390.2:c.427G>A

**Uncertain Significance**

**Met criteria codes** 3

PS4_Moderate PP3 PM2_Supporting

**Not Met criteria codes** 7

BP4 PS1 PS2 PS3 PP1 PM6 PM5

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.3733G>A (p.E143K) variant in MT-ND1 has been reported in 10 individuals with features of primary mitochondrial disease from 4 families. Affected individuals had features consistent with LHON and LHON-plus (PS4_moderate; PMIDs: 15505787, 27177320, 29387390). There are no reports of de novo occurrences of this variant. Segregation was only seen in one family, with healthy mother having lower heteroplasmy levels than affected child (PMID: 15505787), however this does not meet criteria for PP1_supporting (minimum 2 segregations). There are 2 occurrences of this variant in GenBank dataset, however both are from individuals with known mitochondrial disease, and this variant is absent in gnomAD v3.1.2 and in Helix dataset (PM2_supporting). There are no functional studies reported. The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.79 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). 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 Mitochondrial Disease Variant Curation Expert Panel on March 22, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied: PS4_moderate, PM2_supporting, PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PS4_Moderate** | ✔ | The m.3733G>A (p.E143K) variant in MT-ND1 has been reported in 4 individuals with primary mitochondrial disease who had features consistent with LHON (3/4) and LHON-plus (1/4); (PS4_moderate; PMIDs: 15505787, 27177320, 29387390). |
| **PP3** | ✔ | The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.79 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). |
| **PM2_Supporting** | ✔ | There are 2 occurrences in GenBank dataset, however both appear to be from Achilli et al, where the first two cases reported in Valentino et al., 2004 are again discussed. This variant is absent in gnomAD and Helix datasets. |

**Not Met criteria codes**

| | | |
|---|---|---|
| **BP4** | ✖ | The computational predictor APOGEE gives a consensus rating of pathogenic with a score of 0.79 (Min=0, Max=1), which predicts a damaging effect on gene function (PP3). |
| **PS1** | ✖ | No other variants resulting in the same amino acid change have been reported. |
| **PS2** | ✖ | There are no reports of de novo occurrences. |
| **PS3** | ✖ | No functional validation has been performed to date. |
| **PP1** | ✖ | Segregation was only seen in one family, with healthy mother with lower heteroplasmy levels than affected child (PMID: 15505787), however this does not meet criteria for PP1_supporting (minimum 2 segregations). |
| **PM6** | ✖ | There are no reports of de novo occurrences. |
| **PM5** | ✖ | m.3733G>A (p.E143Q) has been reported in one individual (PMID: 22879922) however this variant is not definitively pathogenic. |

Curation History

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