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Variant: NM_000261.2:c.1496T>G

Version: 2.0

CA343722837

1686793 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: a215a4e6-5a7d-4bee-9d62-6a854b218b95
Approved on: 2026/2/19
Published on: 2026/2/18

HGVS expressions

NM_000261.2:c.1496T>G
NC_000001.11:g.171635944A>C
CM000663.2:g.171635944A>C
NC_000001.10:g.171605084A>C
CM000663.1:g.171605084A>C
NC_000001.9:g.169871707A>C
NG_008859.1:g.21690T>G
ENST00000037502.11:c.1496T>G
ENST00000637303.1:c.235-2686A>C
ENST00000638471.1:c.*834T>G
ENST00000037502.10:c.1496T>G
ENST00000614688.1:c.*460T>G
NM_000261.1:c.1496T>G

Likely Pathogenic

Met criteria codes 5

PP3_Moderate PM2_Supporting PS3_Supporting PS4_Supporting PM5_Supporting

Not Met criteria codes 9

PS1 PS2 PP1 PM4 BA1 BS1 BS3 BP7 BP4

Evidence Links 0

Expert Panel

Glaucoma VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Glaucoma Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MYOC Version 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Glaucoma VCEP

The c.1496T>G variant in MYOC is a missense variant predicted to cause substitution of Isoleucine by Serine at amino acid 499 (p.Ile499Ser). The highest minor allele frequency of this variant was in the European (non-Finnish) genetic ancestry group of gnomAD (v4.1.0) = 0.000001695 (2 alleles out of 1,180,016), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.798, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Ile499Ser protein had increased insolubility levels compared to wild type myocilin protein in this study

(PMID: 11004290). The assay met the OddsPath threshold for PS3_Supporting (> 2.1) (when combined with PMID: 10545602) indicating that this variant did impact protein function. Only 1 segregation had been reported for juvenile open angle glaucoma (PMID: 11004290), not meeting the ≥ 3 segregations required for PP1. 2 probands with juvenile or primary open angle glaucoma have been reported carrying this variant (PMID: 11004290 and ANZRAG database [E. Souzeau pers. comm.]), which met PS4_Supporting (≥ 2 probands). Another missense variant (c.1495A>T, p.Ile499Phe, Grantham score = 21, ClinVarID: 1686792) in the same codon has been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1496T>G, p.Ile499Ser variant has a higher Grantham score (= 142) than the previously classified amino acid change, was not predicted to affect splicing as assessed with SpliceAI (≤ 0.2), and met PP3, meeting the conditions for PM5_Supporting to apply. In summary, this variant met the criteria to receive a score of 6 and to be classified as likely pathogenic (likely pathogenic classification range 6 to 9, adapted from PMID: 32720330) for juvenile open angle glaucoma based on the ACMG/AMP criteria met, as specified by the ClinGen Glaucoma VCEP (v2.0.0, 5 Dec 2024): PP3_Moderate, PS3_Supporting, PS4_Supporting, PM2_Supporting, PM5_Supporting

Met criteria codes

PP3_Moderate	✔	The REVEL score = 0.798, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.
PM2_Supporting	✔	The highest minor allele frequency of this variant was in the European (non-Finnish) genetic ancestry group of gnomAD (v4.1.0) = 0.000001695 (2 alleles out of 1,180,016), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles.
PS3_Supporting	✔	The Ile499Ser protein had increased insolubility levels compared to wild type myocilin protein in this study (PMID: 11004290). The assay met the OddsPath threshold for PS3_Supporting (> 2.1) (when combined with PMID: 10545602) indicating that this variant did impact protein function.
PS4_Supporting	✔	2 probands with juvenile or primary open angle glaucoma have been reported carrying this variant (PMID: 11004290 and ANZRAG database [E. Souzeau pers. comm.]), which met PS4_Supporting (≥ 2 probands).
PM5_Supporting	✔	Another missense variant (c.1495A>T, p.Ile499Phe, Grantham score = 21, ClinVarID: 1686792) in the same codon has been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1496T>G, p.Ile499Ser variant has a higher Grantham score (= 142) than the previously classified amino acid change, was not predicted to affect splicing as assessed with SpliceAI (≤ 0.2), and met PP3, meeting the conditions for PM5_Supporting to apply.

Not Met criteria codes

PS1	✖	An established LP or P variant causing this same amino acid change has not been identified.
PS2	✖	This variant has not been identified de novo.
PP1	✖	Only 1 segregation had been reported for juvenile open angle glaucoma (PMID: 11004290), not meeting the ≥ 3 segregations required for PP1.
PM4	✖	This variant does not cause a protein length change.

BA1		✖	This criterion was not met as PM2_Supporting has been met.
BS1		✖	This criterion was not met as PM2_Supporting has been met.
BS3		✖	This criterion was not met as PS3_Supporting has been met.
BP7		✖	This is not an intronic, synonymous or non-coding variant.
BP4		✖	This criterion was not met as PP3 has been met.

Curation History

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