

Variant: *NM_000261.2:c.1442C>G*

Version: 2.0

CA343723138 [↗](#)

1686790 (ClinVar) [↗](#)

Gene: MYOC ([HGNC:4653](#))

Condition: open-angle glaucoma ([MONDO:0005338](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 188e2f43-6748-43da-90e3-d9806858bc6b

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HGVS expressions

NM_000261.2:c.1442C>G

NC_000001.11:g.171635998G>C

CM000663.2:g.171635998G>C

NC_000001.10:g.171605138G>C

CM000663.1:g.171605138G>C

NC_000001.9:g.169871761G>C

NG_008859.1:g.21636C>G

ENST00000037502.11:c.1442C>G

ENST00000637303.1:c.235-2632G>C

ENST00000638471.1:c.*780C>G

ENST00000037502.10:c.1442C>G

ENST00000614688.1:c.*406C>G

NM_000261.1:c.1442C>G

Uncertain Significance

Met criteria codes **3**

PP3_Moderate

PM2_Supporting

PM5_Supporting

Not Met criteria codes **11**

BS1

BS3

BP7

BP4

PS1

PS2

PS3

PS4

BA1

PP1

PM4

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.1442C>G variant in MYOC is a missense variant predicted to cause substitution of Proline by Arginine at amino acid 481 (p.Pro481Arg). This variant was not found in any genetic ancestry group of gnomAD (v4.1.0), meeting the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.853, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. There was no functional evidence predicting a damaging or benign impact of this variant on MYOC function. Only 1 proband with primary open angle glaucoma had been reported (PMID: 12789574), not

meeting the ≥ 2 probands threshold required to meet PS4_Supporting. Another missense variant (c.1442C>T, p.Pro481Leu, Grantham score = 98, ClinVar ID: 1686789) at the same codon has been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1442C>G, p.Pro481Arg variant has a higher Grantham score (= 103) 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 4 and to be classified as a variant of uncertain significance (uncertain significance classification range -1 to 5, adapted from PMID: 32720330) for primary 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, PM2_Supporting, PM5_Supporting.

Met criteria codes

PP3_Moderate			The REVEL score = 0.853, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.
PM2_Supporting			This variant was not found in any genetic ancestry group of gnomAD (v4.1.0), meeting the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles.
PM5_Supporting			Another missense variant (c.1442C>T, p.Pro481Leu, Grantham score = 98, ClinVar ID: 1686789) at the same codon has been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1442C>G, p.Pro481Arg variant has a higher Grantham score (= 103) 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

BS1			This criterion was not met as PM2_Supporting has been met.
BS3			No functional evidence has been found for this variant.
BP7			This criterion did not apply to this variant.
BP4			This criterion was not met as PP3_Moderate has been met.
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.
PS3			No functional evidence has been found for this variant.
PS4			Only 1 proband with POAG had been reported (PMID: 12789574), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting.
BA1			This criterion was not met as PM2_Supporting has been met.

