

Variant: *NM_000261.2:c.1441C>T*

Version: 2.0

CA1244022 [↗](#)

1686786 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: bf05c3e4-02c8-4fe4-83d8-8fbebe319aba

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HGVS expressions

NM_000261.2:c.1441C>T

NC_000001.11:g.171635999G>A

CM000663.2:g.171635999G>A

NC_000001.10:g.171605139G>A

CM000663.1:g.171605139G>A

NC_000001.9:g.169871762G>A

NG_008859.1:g.21635C>T

ENST00000037502.11:c.1441C>T

ENST00000637303.1:c.235-2631G>A

ENST00000638471.1:c.*779C>T

ENST00000037502.10:c.1441C>T

ENST00000614688.1:c.*405C>T

NM_000261.1:c.1441C>T

Uncertain Significance

Met criteria codes **2**

PM2_Supporting PP3

Not Met criteria codes **12**

BA1 BP7 BP4 BS1 BS3 PP1
PS1 PS2 PS3 PS4 PM5
PM4

Evidence Links **1**

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.1441C>T variant in MYOC is a missense variant predicted to cause substitution of Proline by Serine at amino acid 481 (p.Pro481Ser). The highest minor allele frequency of this variant was in the East Asian genetic ancestry group of gnomAD (v4.1.0) = 0.00008911 (4 alleles out of 44,888), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.684, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function. The Pro481Ser protein was assessed in an assay (PMID: 35196929), however, the results for this protein were inconsistent and not included as evidence. Only 1

proband with primary open angle glaucoma had been reported (PMID:15534471), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting. In summary, this variant met the criteria to receive a score of 2 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, PM2_Supporting.

Met criteria codes

PM2_Supporting			The highest minor allele frequency of this variant was in the East Asian genetic ancestry group of gnomAD (v4.1.0) = 0.00008911 (4 alleles out of 44,888), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles.
PP3			The REVEL score = 0.684, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function.

Not Met criteria codes

BA1			This criterion was not met as PM2_Supporting has been met.
BP7			This criterion did not apply to this variant.
BP4			This criterion was not met as PP3 has been met.
BS1			This criterion was not met as PM2_Supporting has been met.
BS3			The Pro481Ser protein was assessed in an assay (PMID: 35196929), however, the results for this protein were inconsistent and not included as evidence.
			The results for the Pro481Ser protein were inconsistent and not included as evidence. PubMed:35196929 
PP1			No segregations have been reported for this variant.
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			The Pro481Ser protein was assessed in an assay (PMID: 35196929), however, the results for this protein were inconsistent and not included as evidence.
			The results for the Pro481Ser protein were inconsistent and not included as evidence. PubMed:35196929 
PS4			Only 1 proband with POAG had been reported (PMID: 15534471), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting.

PM5			PM5_Supporting could not be applied to this novel missense variant as although it did meet PP3, the Grantham score was lower (= 74) than the score for the different missense change at the same amino acid residue determined to be likely pathogenic by the ClinGen Glaucoma VCEP (c.1442C>T, p.Pro481Leu, Grantham score =98, ClinVar ID: 1686789).
PM4			This criterion did not apply to this variant.

Curation History 		
Showing 1 to 2 of 2 rows		

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