

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

Version: 2.0

CA343723135 [↗](#)

1686789 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: a3d0ac6f-9515-4a63-baa8-b0ead4e60a8b

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HGVS expressions

NM_000261.2:c.1442C>T

NC_000001.11:g.171635998G>A

CM000663.2:g.171635998G>A

NC_000001.10:g.171605138G>A

CM000663.1:g.171605138G>A

NC_000001.9:g.169871761G>A

NG_008859.1:g.21636C>T

ENST00000037502.11:c.1442C>T

ENST000000637303.1:c.235-2632G>A

ENST000000638471.1:c.*780C>T

ENST00000037502.10:c.1442C>T

ENST000000614688.1:c.*406C>T

NM_000261.1:c.1442C>T

Likely Pathogenic

Met criteria codes 5

PP1

PP3

PS3_Moderate

PS4_Supporting

PM2_Supporting

Not Met criteria codes 9

PS1

PS2

BA1

BS1

BS3

PM5

PM4

BP7

BP4

Evidence Links 3

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>T variant in MYOC is a missense variant predicted to cause substitution of Proline by Leucine at amino acid 481 (p.Pro481Leu). 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 = 0.72, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function. The Pro481Leu protein had increased instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 21612213, 23129764). The assays met the OddsPath threshold

for PS3_Moderate (> 4.3), indicating that this variant did impact protein function. 3 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 12189160), which fulfilled PP1 (3-4 meioses). 2 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 10196380, 12189160), which met PS4_Supporting (≥ 2 probands). 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): PS3_Moderate, PP1, PP3, PS4_Supporting, PM2_Supporting.

Met criteria codes

PP1		✓	3 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 12189160), which fulfilled PP1 (3-4 meioses).
PP3		✓	The REVEL score = 0.72, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function.
PS3_Moderate		✓	<p>The Pro481Leu protein had increased instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function.</p> <hr/> <p>The Pro481Leu protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 20334347, 23129764, 25524706, 36579626). PubMed:21612213 </p> <p>The Pro481Leu protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 20334347, 21612213, 25524706, 36579626). PubMed:23129764 </p> <p>Note: this is a duplicated result from PMID: 23129764 PubMed:25524706 </p>
PS4_Supporting		✓	2 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 10196380, 12189160), which met PS4_Supporting (≥ 2 probands).
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.

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.
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_Moderate has been met.
PM5		✗	No other LP or P missense variants at this amino acid residue have been identified.

PM4			This criterion did not apply to this variant.
BP7			This criterion did not apply to this variant.
BP4			This criterion was not met as PP3 has been met.

Curation History 		
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