

Variant: *NM\_000261.2:c.1495A>T*

Version: 2.0

CA343722844 [↗](#)

1686792 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal dominant inheritance

**UUID:** c2449615-dd58-4ce4-be85-4655d3043e9b

**Approved on:** 2026/1/13

**Published on:** 2026/1/12

### HGVS expressions

**NM\_000261.2:c.1495A>T**

NC\_000001.11:g.171635945T>A

CM000663.2:g.171635945T>A

NC\_000001.10:g.171605085T>A

CM000663.1:g.171605085T>A

NC\_000001.9:g.169871708T>A

NG\_008859.1:g.21689A>T

ENST00000037502.11:c.1495A>T

ENST00000637303.1:c.235-2685T>A

ENST00000638471.1:c.\*833A>T

ENST00000037502.10:c.1495A>T

ENST00000614688.1:c.\*459A>T

NM\_000261.1:c.1495A>T

**Likely Pathogenic**

**Met criteria codes** 5

PP1\_Moderate

PP3

PS3\_Moderate

PS4\_Supporting

PM2\_Supporting

**Not Met criteria codes** 9

PS1

PS2

BA1

BS1

BS3

PM5

PM4

BP7

BP4

**Evidence Links** 4

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.1495A>T variant in MYOC is a missense variant predicted to cause substitution of Isoleucine by Phenylalanine at amino acid 499 (p.Ile499Phe). This variant was not found in any genetic ancestry group of gnomAD (v4.1.0), meeting the  $\leq 0.0001$  threshold set for PM2\_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.67, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function. The Ile499Phe 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. This protein has also been assessed in these other studies (PMIDs: 24333014, 10545602, 16297911), however, the same level of evidence was not met. 6 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 9328473), which fulfilled PP1\_Moderate (5-6 meioses). 2 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 12872267, 9328473), which met PS4\_Supporting (≥ 2 probands). In summary, this variant met the criteria to receive a score of 7 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\_Moderate, PP3, PS4\_Supporting, PM2\_Supporting

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP1_Moderate   |    |    | 6 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 9328473), which fulfilled PP1_Moderate (5-6 meioses).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| PP3            |    |    | The REVEL score = 0.67, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| PS3_Moderate   |    |    | <p>The Ile499Phe 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 (&gt; 4.3), indicating that this variant did impact protein function. This protein has also been assessed in these other studies (PMIDs: 24333014, 10545602, 16297911), however, the same level of evidence was not met.</p> <hr/> <p>The I499F protein is unstable. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (&gt; 2.1). <a href="#">PubMed:24333014</a> </p> <p>The I499F protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (&gt; 4.3) (when combined with PMIDs: 20334347, 21612213, 25524706, 36579626). <a href="#">PubMed:23129764</a> </p> <p>The I499F protein is unstable. Note: this is a duplicated result from PMID: 23129764 <a href="#">PubMed:25524706</a> </p> <p>The I499F protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (&gt; 4.3) (when combined with PMIDs: 20334347, 23129764, 25524706, 36579626). <a href="#">PubMed:21612213</a> </p> |
| PS4_Supporting |  |  | 2 probands with juvenile or primary open angle glaucoma have been reported carrying this variant (PMIDs: 12872267, 9328473), 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.                                  |

|            |                                                                                   |   |                                                                                                                                                                                                                                                                                                                                     |
|------------|-----------------------------------------------------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>BS3</b> |                                                                                   | ✖ | This criterion was not met as PS3_Moderate has been met.                                                                                                                                                                                                                                                                            |
| <b>PM5</b> |  | ✖ | PM5_Supporting could not be applied to this novel missense variant as although it did meet PP3, the Grantham score was lower (= 21) 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.1496T>G, p.Ile499Ser, Grantham score = 142). |
| <b>PM4</b> |  | ✖ | This variant does not cause a protein length change.                                                                                                                                                                                                                                                                                |
| <b>BP7</b> |  | ✖ | This is not an intronic, synonymous or non-coding variant.                                                                                                                                                                                                                                                                          |
| <b>BP4</b> |  | ✖ | This criterion was not met as PP3 has been met.                                                                                                                                                                                                                                                                                     |

Curation History 

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