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Variant: NM_000261.2(MYOC):c.1430T>G (p.Ile477Ser)

Version: 2.0

CA119174

7950 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6e296ba8-41a9-4f53-b189-0d71102717a4
Approved on: 2026/2/19
Published on: 2026/2/18

HGVS expressions

NM_000261.2:c.1430T>G
NM_000261.2(MYOC):c.1430T>G (p.Ile477Ser)
NC_000001.11:g.171636010A>C
CM000663.2:g.171636010A>C
NC_000001.10:g.171605150A>C
CM000663.1:g.171605150A>C
NC_000001.9:g.169871773A>C
NG_008859.1:g.21624T>G
ENST00000037502.11:c.1430T>G
ENST00000637303.1:c.235-2620A>C
ENST00000638471.1:c.*768T>G
ENST00000037502.10:c.1430T>G
ENST00000614688.1:c.*394T>G
NM_000261.1:c.1430T>G

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PS3_Moderate PP1_Moderate

Not Met criteria codes 10

BA1 PM5 PM4 BS1 BS3 PS1 PS2 PS4 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.1430T>G variant in MYOC is a missense variant predicted to cause substitution of Isoleucine by Serine at amino acid 477 (p.Ile477Ser). 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 = 0.646, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function. The Ile477Ser protein had increased instability compared to wild type myocilin

protein in these studies (PMIDs: 20334347, 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: 10545602, 11152659, 14688426, 16297911), however, the same level of evidence was not met. 20 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 9328473), which fulfilled PP1_Moderate (≥5 meioses in ≥1 family, but not the ≥7 meioses in >1 family for the strong criterion). Only 1 proband with JOAG had been reported (PMID: 9328473), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting. 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_Moderate, PP3, PM2_Supporting.

Met criteria codes

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.
PP3	✔	The REVEL score = 0.646, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function.
PS3_Moderate	✔	The Ile477Ser protein had increased instability compared to wild type myocilin protein in these studies (PMIDs: 20334347, 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: 10545602, 11152659, 14688426, 16297911), however, the same level of evidence was not met. The Ile477Ser protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 21612213, 23129764, 25524706, 36579626). PubMed:20334347 The Ile477Ser 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 The Ile477Ser protein has reduced secretion. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:14688426 The Ile477Ser 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
PP1_Moderate	✔	20 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 9328473), which fulfilled PP1_Moderate (≥5 meioses in ≥1 family, but not the ≥7 meioses in >1 family for the strong criterion).

Not Met criteria codes

BA1	✖	This criterion was not met as PM2_Supporting has been met.
PM5	✖	PM5_Supporting could not be applied to this novel missense variant as although it did meet PP3, the Grantham score was lower (= 142) 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.1430T>A, p.Ile477Asn, Grantham score = 149, ClinVar ID: 30205).
PM4	✖	This criterion did not apply to this variant.

BS1		✖	This criterion was not met as PM2_Supporting has been met.
BS3		✖	This criterion was not met as PS3_Supporting 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.
PS4		✖	Only 1 proband with JOAG had been reported (PMID: 9328473), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting.
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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