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Variant: NM_000261.2(MYOC):c.1430T>A (p.Ile477Asn)

Version: 2.0

CA129023

30205 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5fe3a673-abb3-4cde-a22c-baa28336fbe7
Approved on: 2025/11/13
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HGVS expressions

NM_000261.2(MYOC):c.1430T>A (p.Ile477Asn)
NM_000261.2:c.1430T>A
NC_000001.11:g.171636010A>T
CM000663.2:g.171636010A>T
NC_000001.10:g.171605150A>T
CM000663.1:g.171605150A>T
NC_000001.9:g.169871773A>T
NG_008859.1:g.21624T>A
ENST00000037502.11:c.1430T>A
ENST00000637303.1:c.235-2620A>T
ENST00000638471.1:c.*768T>A
ENST00000037502.10:c.1430T>A
ENST00000614688.1:c.*394T>A
NM_000261.1:c.1430T>A

Likely Pathogenic

Met criteria codes 4

PP1_Strong PS3_Moderate PS4_Supporting PM2_Supporting

Not Met criteria codes 10

PM5 PM4 BA1 BS1 BS3 BP7 BP4 PS1 PS2 PP3

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.1430T>A variant in MYOC is a missense variant predicted to cause substitution of Isoleucine by Asparagine at amino acid 477 (p.Ile477Asn). 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 = 0.534, which was neither above nor below the thresholds for PP3 (≥ 0.644) or BP4 (≤ 0.290), predicting a damaging or benign impact on MYOC function. The Ile477Asn protein had

increased insolubility, instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 20334347, 21612213, 23129764, 36267417). 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, 11004290, 16297911, 27092720), however, the same level of evidence was not met. 34 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 9754180, 9535666), which fulfilled PP1_Strong (≥7 meioses in >1 family). 3 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 9754180, 9535666, ARVO Abstract), which met PS4_Supporting (≥ 2 probands). In summary, this variant met the criteria to receive a score of 8 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): PP1_Strong, PS3_Moderate, PS4_Supporting, PM2_Supporting.

Met criteria codes

PP1_Strong	✔	34 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 9754180, 9535666), which fulfilled PP1_Strong (≥7 meioses in >1 family).
PS3_Moderate	✔	The Ile477Asn protein had increased insolubility, instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 20334347, 21612213, 23129764, 36267417). 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, 11004290, 16297911, 27092720), however, the same level of evidence was not met.
PS4_Supporting	✔	3 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 9754180, 9535666, ARVO Abstract), 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

PM5	✖	PM5_Supporting could not be applied to this novel missense variant as, although the Grantham score was higher (= 149) 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>G, p.Ile477Ser, Grantham score = 142), it did not meet PP3.
PM4	✖	This criterion did not apply to this variant.
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.
BP7	✖	This criterion did not apply to this variant.
BP4	✖	The REVEL score = 0.534, which did not meet the ≤ 0.290 threshold required for BP4.

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.
PP3		✖	The REVEL score = 0.534, which did not meet the ≥ 0.644 threshold required for PP3.

Curation History

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