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Variant: NM_000261.2:c.1130C>T

Version: 2.0

CA1244075

1342202 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: c1e7d5a4-2952-462d-95e6-714568dcbcd0
Approved on: 2026/1/19
Published on: 2026/1/21

HGVS expressions

NM_000261.2:c.1130C>T
NC_000001.11:g.171636310G>A
CM000663.2:g.171636310G>A
NC_000001.10:g.171605450G>A
CM000663.1:g.171605450G>A
NC_000001.9:g.169872073G>A
NG_008859.1:g.21324C>T
ENST00000037502.11:c.1130C>T
ENST00000637303.1:c.235-2320G>A
ENST00000638471.1:c.*468C>T
ENST00000037502.10:c.1130C>T
ENST00000614688.1:c.*94C>T
NM_000261.1:c.1130C>T

Pathogenic

Met criteria codes 6

PS3_Moderate PP1_Strong PM2_Supporting PM5_Supporting PS4 PP3_Moderate

Not Met criteria codes 8

BS1 BS3 BP7 BP4 BA1 PM4 PS1 PS2

Evidence Links 5

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.1130C>T variant in MYOC is a missense variant predicted to cause substitution of Threonine by Methionine at amino acid 377 (p.Thr377Met). The highest minor allele frequency of this variant was in the African/African American genetic ancestry group of gnomAD (v4.1.0) = 0.00002668 (2 alleles out of 74,972), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.924, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Thr377Met protein had increased instability levels compared to wild type myocilin protein in these studies (PMIDs:

21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3) indicating that this variant did impact protein function. The assays reporting solubility and secretion evidence (PMIDs: 11004290, 10545602, 16297911, 16466712) indicated that this variant may impact protein solubility and secretion, however, as the results were conflicting and inconclusive, this evidence was not included. 47 segregations in 6 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 20390039, 11004290, 28564705, 15823921, 12912696), which fulfilled PP1_Strong (≥7 meioses in >1 family). There were more family studies published than presented here. 15 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 28564705, 22933836, 11004290, 12868033, 20390039, 14627955, 10196380, 15823921, 12912696), which met PS4 (≥ 15 probands). There were more probands published than presented here. Another missense variant (c.1130C>A, p.Thr377Lys, Grantham score = 78, ClinVar ID: 2500837) at the same codon has been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1130C>T, p.Thr377Met variant has a higher Grantham score (= 81) than the previously classified amino acid change, was not predicted to affect splicing as assessed with SpliceAI (≤ 0.2), and met PP3, meeting the conditions for PM5_Supporting to apply. In summary, this variant met the criteria to receive a score of 14 and to be classified as pathogenic (pathogenic classification ≥ 10, 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): PS4, PP1_Strong, PS3_Moderate, PP3_Moderate, PM2_Supporting, PM5_Supporting

Met criteria codes

PS3_Moderate ✔

The Thr377Met protein had increased instability levels compared to wild type myocilin protein in these studies (PMIDs: 21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3) indicating that this variant did impact protein function. The assays reporting solubility and secretion evidence (PMIDs: 11004290, 10545602, 16297911, 16466712) indicated that this variant may impact protein solubility and secretion, however, the results were either inconclusive, did not meet the same level of evidence, or were overridden by the stability assays results.

The T377M protein is unstable. Note: this is a duplicated result from PMID: 23129764 PubMed:25524706
The T377M 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
The T377M 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 T377M protein is insoluble. The assay in this study meets the OddsPath threshold for PS3_Supporting (> 2.1) (when combined with PMID: 10545602) but not the threshold for PS3_Moderate (> 4.3). PubMed:11004290
The T377M protein demonstrated partial solubility. The assay in this study meets the OddsPath threshold for PS3_Supporting (> 2.1) (when combined with PMID: 11004290) but not the threshold for PS3_Moderate (> 4.3). PubMed:10545602

PP1_Strong ✔

47 segregations in 6 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 20390039, 11004290, 28564705, 15823921, 12912696), which fulfilled PP1_Strong (≥7 meioses in >1 family). There were more family studies published than presented here.

PM2_Supporting ✔

The highest minor allele frequency of this variant was in the African/African American genetic ancestry group of gnomAD (v4.1.0) = 0.00002668 (2 alleles out of 74,972), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles.

PM5_Supporting ✔

Another missense variant (c.1130C>A, p.Thr377Lys, Grantham score = 78, ClinVar ID: 2500837) at the same codon has been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1130C>T, p.Thr377Met variant has a higher Grantham score (= 81) than the previously classified amino acid change, was not predicted to affect splicing as assessed with SpliceAI (≤ 0.2), and met PP3, meeting the conditions for PM5_Supporting to apply.

PS4	✔	15 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 28564705, 22933836, 11004290, 12868033, 20390039, 14627955, 10196380, 15823921, 12912696), which met PS4 (≥ 15 probands). There were more probands published than presented here.
PP3_Moderate	✔	The REVEL score = 0.924, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.

Not Met criteria codes

BS1	✖	This criterion was not met as PM2_Supporting has been met.
BS3	✖	This criterion was not met as PS3 has been met.
BP7	✖	This is not an intronic, synonymous or non-coding variant.
BP4	✖	This criterion was not met as PP3 has been met.
BA1	✖	This criterion was not met as PM2_Supporting has been met.
PM4	✖	This variant does not cause a protein length change.
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.

Curation History

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