The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000261.2(MYOC):c.1109C>T (p.Pro370Leu)

Version: 2.0

CA119171

7948 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 924d6dc0-3570-496f-a90d-2cb4cd205f2f
Approved on: 2025/12/4
Published on: 2025/12/4

HGVS expressions

NM_000261.2:c.1109C>T
NM_000261.2(MYOC):c.1109C>T (p.Pro370Leu)
NC_000001.11:g.171636331G>A
CM000663.2:g.171636331G>A
NC_000001.10:g.171605471G>A
CM000663.1:g.171605471G>A
NC_000001.9:g.169872094G>A
NG_008859.1:g.21303C>T
ENST00000037502.11:c.1109C>T
ENST00000637303.1:c.235-2299G>A
ENST00000638471.1:c.*447C>T
ENST00000037502.10:c.1109C>T
ENST00000614688.1:c.*73C>T
NM_000261.1:c.1109C>T

Pathogenic

Met criteria codes 5

PP1_Strong PS3 PS4 PP3_Moderate PM2_Supporting

Not Met criteria codes 9

BA1 PM5 PM4 BS1 BS3 PS1 PS2 BP4 BP7

Evidence Links 9

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.1109C>T variant in MYOC is a missense variant predicted to cause substitution of Proline by Leucine at amino acid 370 (p.Pro370Leu). 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 = 0.89, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. A transgenic mouse model carrying human MYOC Pro370Leu (PMID:

36069958), and displaying reduced secretion of the Pro370Leu protein in vivo, exhibited a glaucoma phenotype (IOP elevation and retinal ganglion cell loss), meeting PS3. The Pro370Leu protein has also been assessed in these solubility, stability and secretion studies (PMIDs: 16466712,10545602, 11004290, 36579626, 15069026,16297911, 19234343, 17615537, 36267417, 21612213, 31270212), however, the same level of evidence was not met. 21 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 9490287, 9772276), 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: 9345106, 9328473, 11774072, 28564705, 12447164, 22194650, 9792882, 23453510, 29540704, 30484747, 9490287, 9772276), which met PS4 (≥ 15 probands). There were more probands published than presented here. In summary, this variant met the criteria to receive a score of 15 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, new_date_2024): PS3, PS4, PP1_Strong, PP3_Moderate, PM2_Supporting

Met criteria codes

PP1_Strong ✔

21 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 9490287, 9772276), which fulfilled PP1_Strong (≥7 meioses in >1 family). There were more family studies published than presented here.

PS3 ✔

A transgenic mouse model carrying human MYOC Pro370Leu (PMID: 36069958), and displaying reduced secretion of the Pro370Leu protein in vivo, exhibited a glaucoma phenotype (IOP elevation and retinal ganglion cell loss), meeting PS3. The Pro370Leu protein has also been assessed in these solubility, stability and secretion studies (PMIDs: 16466712,10545602, 11004290, 36579626, 15069026,16297911, 19234343, 17615537, 36267417, 21612213, 31270212), however, the same level of evidence was not met.

The P370L protein is insoluble. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:19234343
The P370L 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
A transgenic mouse model carrying human MYOC P370L and displaying reduced secretion of P370L protein in vivo exhibited a glaucoma phenotype (IOP elevation, retina ganglion cell loss) PubMed:36069958
The P370L protein is insoluble. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:17615537
Although the P370L protein was assayed in this study, its levels were too low to be detected and were not included as evidence. PubMed:21612213
Although the P370L protein was assayed in this study, its levels were too low to be detected and were not included as evidence. PubMed:31270212
The P370L protein is insoluble. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:15069026
The P370L protein has reduced secretion. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3). PubMed:36267417
The P370L protein was assessed in this assay, however, the results of this study were inconsistent and functional evidence was not included. PubMed:36579626

PS4 ✔

15 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 9345106, 9328473, 11774072, 28564705, 12447164, 22194650, 9792882, 23453510, 29540704, 30484747, 9490287, 9772276), which met PS4 (≥ 15 probands). There were more probands published than presented here.

PP3_Moderate ✔

The REVEL score = 0.89, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.

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

BA1	✖	This criterion was not met as PM2_Supporting has been met.
PM5	✖	No other LP or P missense variants at this amino acid residue have been identified.
PM4	✖	This variant does not cause a protein length change.
BS1	✖	This criterion was not met as PM2_Supporting has been met.
BS3	✖	This criterion was not met as PS3_Moderate 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.
BP4	✖	This criterion was not met as PP3 has been met.
BP7	✖	This is not an intronic, synonymous or non-coding variant.

Curation History

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