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:c.761C>T

Version: 2.0

CA343726245

1342967 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8d13c39d-90c0-4a37-af54-854d4349e596
Approved on: 2026/1/13
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HGVS expressions

NM_000261.2:c.761C>T
NC_000001.11:g.171636679G>A
CM000663.2:g.171636679G>A
NC_000001.10:g.171605819G>A
CM000663.1:g.171605819G>A
NC_000001.9:g.169872442G>A
NG_008859.1:g.20955C>T
ENST00000037502.11:c.761C>T
ENST00000637303.1:c.235-1951G>A
ENST00000638471.1:c.*99C>T
ENST00000037502.10:c.761C>T
ENST00000614688.1:c.761C>T
NM_000261.1:c.761C>T

Likely Pathogenic

Met criteria codes 5

PS3_Moderate PS2_Moderate PM2_Supporting PM5_Supporting PP3_Moderate

Not Met criteria codes 9

BS1 BS3 BP7 BP4 BA1 PM4 PS1 PS4 PP1

Evidence Links 1

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.761C>T variant in MYOC is a missense variant predicted to cause substitution of Proline by Leucine at amino acid 254 (p.Pro254Leu). 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 = 0.925, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Pro254Leu protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in this study (PMID: 35196929). The assay met the OddsPath threshold for PS3_Moderate (> 4.3), indicating

that this variant did impact protein function. A confirmed de novo proband with juvenile open angle glaucoma was identified (PMID: 27080696), meeting PS2_Moderate. However, as this was the only proband identified, the ≥ 2 probands threshold required to meet PS4_Supporting was not met. 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): PS2_Moderate, PS3_Moderate, PP3_Moderate, PM2_Supporting, PM5_Supporting.

Met criteria codes

PS3_Moderate	✔	The Pro254Leu protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in this study (PMID: 35196929). The assay met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function. The Pro254Leu protein is insoluble and has reduced secretion. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3). PubMed:35196929
PS2_Moderate	✔	1 confirmed de novo proband with JOAG has been identified.
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.
PM5_Supporting	✔	Another missense variant (c.760C>A, p.Pro254Thr, Grantham score = 38, ClinVar ID: 2429764) at the same codon has been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.761C>T, p.Pro254Leu variant has a higher Grantham score (= 98) 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.
PP3_Moderate	✔	The REVEL score = 0.925, 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_Moderate has been met.
BP7	✖	This criterion did not apply to this 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 criterion did not apply to this variant.

PS1		✖	An established LP or P variant causing this same amino acid change has not been identified.
PS4		✖	Only 1 proband with JOAG had been reported (PMID: 27080696), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting.
PP1		✖	No segregations have been reported for this variant.

Curation History

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