

Variant: NM_000261.2:c.967G>A

Version: 2.0

CA343725312 [↗](#)

1342969 (ClinVar) [↗](#)

Gene: MYOC ([HGNC:4653](#))

Condition: open-angle glaucoma ([MONDO:0005338](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 888624e6-7cfd-465a-b22b-2eb67ffb2a41

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HGVS expressions

NM_000261.2:c.967G>A

NC_000001.11:g.171636473C>T

CM000663.2:g.171636473C>T

NC_000001.10:g.171605613C>T

CM000663.1:g.171605613C>T

NC_000001.9:g.169872236C>T

NG_008859.1:g.21161G>A

ENST00000037502.11:c.967G>A

ENST00000637303.1:c.235-2157C>T

ENST00000638471.1:c.*305G>A

ENST00000037502.10:c.967G>A

ENST00000614688.1:c.967G>A

NM_000261.1:c.967G>A

Likely Pathogenic

Met criteria codes 5

PS3_Moderate

PP3

PS4_Supporting

PP1_Moderate

PM2_Supporting

Not Met criteria codes 9

BP7

BP4

BS1

BS3

PS1

PS2

BA1

PM5

PM4

Evidence Links 3

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.967G>A variant in MYOC is a missense variant predicted to cause substitution of Glutamic Acid by Lysine at amino acid 323 (p.Glu323Lys). 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 = 0.759, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function. The Glu323Lys protein had increased insolubility, instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 21612213, 23129764). The assays met the

OddsPath threshold for PS3_Moderate (> 4.3). This protein has also been assessed in these other studies (PMIDs: 11004290, 10545602, 15069026, 16297911), however, the same level of evidence was not met. 10 segregations in 1 family, with juvenile open angle glaucoma, have been reported (PMID: 9772276), which fulfilled PP1_Moderate (≥ 5 meioses in ≥ 1 family, but not the ≥ 7 meioses in > 1 family for the strong criterion). 5 probands with juvenile or primary open angle glaucoma have been reported carrying this variant (PMIDs: 9772276, 12616399, 37485465), which met PS4_Supporting (≥ 2 probands). In summary, this variant met the criteria to receive a score of 7 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, PS4_Supporting, PM2_Supporting

Met criteria codes

PS3_Moderate			The Glu323Lys protein had increased insolubility, instability and reduced secretion levels compared to wild type myocilin protein in this these studies (PMIDs: 16466712, 10545602, 11004290, 21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3). This protein has also been assessed in these other studies (PMIDs: 15069026, 16297911), however, the same level of evidence was not met. The E32K 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 E32K protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 23129764, 25524706, 36579626, 20334347). PubMed:21612213  The E32K protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 20334347, 21612213, 23129764, 36579626). Note: this is a duplicated result from PMID: 23129764 PubMed:25524706 
PP3			The REVEL score = 0.759, which was within the 0.644-0.772 range for PP3, predicting a damaging effect on MYOC function.
PS4_Supporting			5 probands with juvenile or primary open angle glaucoma have been reported carrying this variant (PMIDs: 9772276, 12616399, 37485465), which met PS4_Supporting (≥ 2 probands).
PP1_Moderate			10 segregations in 1 family, with juvenile open angle glaucoma, have been reported (PMID: 9772276), which fulfilled PP1_Moderate (≥ 5 meioses in ≥ 1 family, but not the ≥ 7 meioses in > 1 family for the strong criterion).
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

BP7			This is not an intronic, synonymous or non-coding variant.
BP4			This criterion was not met as PP3 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.

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.
BA1			This criterion was not met as PM2_Supporting has been met.
PM5			An established LP or P variant causing this same amino acid change has not been identified.
PM4			This variant does not cause a protein length change.

Curation History 		
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