

Variant: *NM_000261.2(MYOC):c.1267A>G (p.Lys423Glu)*

Version: 1.0

[CA119178](#)

[7954 \(ClinVar\)](#)

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

Condition: juvenile open angle glaucoma ([MONDO:0020367](#))

Inheritance Mode: Autosomal dominant inheritance

UID: a688a14d-f3d1-4cd4-acea-a2d22bafb4b0

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HGVS expressions

NM_000261.2:c.1267A>G

NM_000261.2(MYOC):c.1267A>G (p.Lys423Glu)

NC_000001.11:g.171636173T>C

CM000663.2:g.171636173T>C

NC_000001.10:g.171605313T>C

CM000663.1:g.171605313T>C

NC_000001.9:g.169871936T>C

NG_008859.1:g.21461A>G

ENST00000037502.11:c.1267A>G

ENST000000637303.1:c.235-2457T>C

ENST000000638471.1:c.*605A>G

ENST00000037502.10:c.1267A>G

ENST000000614688.1:c.*231A>G

NM_000261.1:c.1267A>G

Likely Pathogenic

Met criteria codes **5**

PP3

PM2_Supporting

PS4_Supporting

PS3_Moderate

PP1_Strong

Not Met criteria codes **10**

BP7

BP4

BS1

BS3

PM6

PS1

PS2

PM5

PM4

BA1

Evidence Links **1**

Expert Panel

[Glaucoma VCEP](#)

Criteria Specification Information

[Criteria Specification:](#) *ClinGen Glaucoma Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1.1*

[PDF](#)

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)












Evidence submitted by expert panel

Glaucoma VCEP













The c.1267A>G variant in MYOC is a missense variant predicted to cause substitution of Lysine by Glutamic Acid at amino acid 423 (p.Lys423Glu). This variant was not found in any population of gnomAD (v2.1.1), meeting the ≤ 0.0001 threshold set for PM2_Supporting in a population of at least 10,000 alleles. The REVEL score = 0.876, which met the ≥ 0.7 threshold for PP3, predicting a damaging effect on







MYOC function. A previous study (PMID: 16466712) demonstrated that the Lys423Glu protein had reduced secretion levels compared to wild type myocilin protein and met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function. 80 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 12860809, 9697688), which fulfilled PP1_Strong (≥ 7 meioses in >1 family). 4 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 30484747, 12189160, 12860809, 9697688), which met PS4_Supporting (≥ 2 probands). In summary, this variant met the criteria to receive a score of 9 and to be classified as likely pathogenic (likely pathogenic classification range 6 to 9) for juvenile open angle glaucoma based on the ACMG/AMP criteria met, as specified by the ClinGen Glaucoma VCEP (v1, 12 Oct 2021): PP1_Strong, PS3_Moderate, PP3, PS4_Supporting, PM2_Supporting

Met criteria codes

PP3			The REVEL score = 0.876, which met the ≥ 0.7 threshold for PP3, predicting a damaging effect on MYOC function.
PM2_Supporting			This variant was not found in any population of gnomAD (v2.1.1), meeting the ≤ 0.0001 threshold set for PM2_Supporting in a population of at least 10,000 alleles.
PS4_Supporting			4 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 30484747, 12189160, 12860809, 9697688), which met PS4_Supporting (≥ 2 probands).
PS3_Moderate			A previous study (PMID: 16466712) demonstrated that the Lys423Glu protein had reduced secretion levels compared to wild type myocilin protein and met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function.
			The K423E protein is insoluble. This study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:15069026 
PP1_Strong			80 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 12860809, 9697688), which fulfilled PP1_Strong (≥ 7 meioses in >1 family).

Not Met criteria codes

BP7			This is not a 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.
PM6			This variant has not been identified de novo.
PS1			An established pathogenic variant causing this same amino acid change has not been identified.
PS2			This variant has not been identified de novo.

PM5			No other missense variants at this amino acid residue have been identified.
PM4			This variant does not cause a protein length change.
BA1			This criterion was not met as PM2_Supporting has been met.

Curation History [↗](#)

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