

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

Version: 2.0

CA119178 [↗](#)

7954 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

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

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HGVS expressions

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

NM_000261.2:c.1267A>G

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

Pathogenic

Met criteria codes 5

PS4_Supporting

PM2_Supporting

PS3_Moderate

PP1_Strong

PP3_Moderate

Not Met criteria codes 9

BS1

BS3

BP4

BP7

PS1

PS2

BA1

PM5

PM4

Evidence Links 0

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.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 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 = 0.876, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Lys423Glu protein had increased insolubility, instability and

reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 36267417, 20334347, 21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function. This protein has also been assessed in these other studies (PMIDs: 10545602, 11152659, 15069026, 16297911), however, the same level of evidence was not met. 82 segregations in 3 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 12860809, 9697688, 37247815), which fulfilled PP1_Strong (≥7 meioses in >1 family). 5 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 30484747, 12189160, 12860809, 9697688, 37247815), which met PS4_Supporting (≥ 2 probands). In summary, this variant met the criteria to receive a score of 10 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): PP1_Strong, PS3_Moderate, PP3_Moderate, PM2_Supporting, PS4_Supporting.

Met criteria codes

PS4_Supporting			5 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 30484747, 12189160, 12860809, 9697688, 37247815), which met PS4_Supporting (≥ 2 probands).
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.
PS3_Moderate			The Lys423Glu protein had increased insolubility, instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 36267417, 20334347, 21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function. This protein has also been assessed in these other studies (PMIDs: 10545602, 11152659, 15069026, 16297911), however, the same level of evidence was not met.
PP1_Strong			82 segregations in 3 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 12860809, 9697688, 37247815), which fulfilled PP1_Strong (≥7 meioses in >1 family).
PP3_Moderate			The REVEL score = 0.876, 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.
BP4			This criterion was not met as PP3 has been met.
BP7			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.
PS2			This variant has not been identified de novo.

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 criterion did not apply to this variant.

Curation History 		
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