

Variant: *NM_000261.2:c.1298G>A*

Version: 2.0

CA343723939 [↗](#)

2500839 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: d06633f1-669c-4aa8-a43d-4f145c930b4e

Approved on: 2026/2/19

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HGVS expressions

NM_000261.2:c.1298G>A

NC_000001.11:g.171636142C>T

CM000663.2:g.171636142C>T

NC_000001.10:g.171605282C>T

CM000663.1:g.171605282C>T

NC_000001.9:g.169871905C>T

NG_008859.1:g.21492G>A

ENST00000037502.11:c.1298G>A

ENST00000637303.1:c.235-2488C>T

ENST00000638471.1:c.*636G>A

ENST00000037502.10:c.1298G>A

ENST00000614688.1:c.*262G>A

NM_000261.1:c.1298G>A

Likely Pathogenic

Met criteria codes **3**

PM2_Supporting

PP3_Strong

PM5

Not Met criteria codes **11**

BS1

BS3

BP4

BP7

PS1

PS2

PS3

PS4

PP1

BA1

PM4

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.1298G>A variant in MYOC is a missense variant predicted to cause substitution of Cysteine by Tyrosine at amino acid 433 (p.Cys433Tyr). 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 = 0.956, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function. The assays in this study (PMID: 40081751), measuring solubility and secretion of the Cys433Tyr protein, did not meet the OddsPath threshold for PS3_Supporting (> 2.1). Only 1 proband with juvenile open angle

glaucoma (JOAG) had been reported (PMID: 33793440), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting. Another missense variant (c.1297T>C, p.Cys433Arg, Grantham score = 180, ClinVar ID: 7956) in the same codon, has been classified as pathogenic for JOAG by the ClinGen Glaucoma VCEP. The c.1298G>A, p.Cys433Tyr variant has a higher Grantham score (= 194) 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 to apply. In summary, this variant met the criteria to receive a score of 6 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): PP3_Strong, PM5, PM2_Supporting (PP3 and PM5 capped at 5 points)

Met criteria codes

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.
PP3_Strong			The REVEL score = 0.956, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function.
PM5			Another missense variant (c.1297T>C, p.Cys433Arg, Grantham score = 180, ClinVar ID: 7956) in the same codon, has been classified as pathogenic for JOAG by the ClinGen Glaucoma VCEP. The c.1298G>A, p.Cys433Tyr variant has a higher Grantham score (= 194) 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 to apply.

Not Met criteria codes

BS1			This criterion was not met as PM2_Supporting has been met.
BS3			Although the OddsPath threshold for PS3_Supporting was not met, this variant may impact protein function (see PS3 comment).
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			The C433Y protein is insoluble in 1 assay and demonstrates reduced secretion and an indeterminate level of solubility in other assays in this study. None of the assays in this study meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:40081751 
BP4			This criterion was not met as PP3 has been met.
BP7			This is not an intronic, synonymous or non-coding 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.
PS3			The assays in this study (PMID: 40081751), measuring solubility and secretion of the Cys433Tyr protein, did not meet the OddsPath threshold for PS3_Supporting (> 2.1).
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			The C433Y protein is insoluble in 1 assay and demonstrates reduced secretion and an indeterminate level of solubility in other assays in this study. None of the assays in this study meet the OddsPath threshold for

PS3_Supporting (> 2.1). PubMed:40081751 ↗			
PS4		✖	Only 1 proband with juvenile open angle glaucoma (JOAG) had been reported (PMID: 33793440), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting.
PP1		✖	No segregations have been reported for this variant.
BA1		✖	This criterion was not met as PM2_Supporting has been met.
PM4		✖	This variant does not cause a protein length change.

Curation History ↗		
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