

Variant: *NM_000261.2(MYOC):c.1297T>C (p.Cys433Arg)*

Version: 2.0

CA119181 [↗](#)

7956 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 17a16a8f-7d35-4be9-9c5a-125f169a53f3

Approved on: 2026/2/5

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HGVS expressions

NM_000261.2:c.1297T>C

NM_000261.2(MYOC):c.1297T>C (p.Cys433Arg)

NC_000001.11:g.171636143A>G

CM000663.2:g.171636143A>G

NC_000001.10:g.171605283A>G

CM000663.1:g.171605283A>G

NC_000001.9:g.169871906A>G

NG_008859.1:g.21491T>C

ENST00000037502.11:c.1297T>C

ENST000000637303.1:c.235-2487A>G

ENST000000638471.1:c.*635T>C

ENST00000037502.10:c.1297T>C

ENST000000614688.1:c.*261T>C

NM_000261.1:c.1297T>C

Pathogenic

Met criteria codes 5

PS3_Moderate PP1_Strong

PM2_Supporting PS4

PP3_Moderate

Not Met criteria codes 9

BS1 BS3 BP7 BP4 PM5

BA1 PM4 PS1 PS2

Evidence Links 4

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.1297T>C variant in MYOC is a missense variant predicted to cause substitution of Cysteine by Arginine at amino acid 433 (p.Cys433Arg). 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 = 0.913, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Cys433Arg protein had increased instability and reduced secretion

levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 36267417, 21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function. 23 segregations in 4 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 10819638, 16936947, 12671463), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family). 30 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 30484747, 10819638, 16936947, 12671463), which met PS4 (≥ 15 probands). In summary, this variant met the criteria to receive a score of 13 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): PS4, PP1_Strong, PS3_Moderate, PP3_Moderate, PM2_Supporting

Met criteria codes

PS3_Moderate			<p>The Cys433Arg protein had increased instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 36267417, 21612213, 23129764). The assays met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function.</p> <p>The C433R protein has reduced secretion. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3). PubMed:36267417 </p> <p>The C433R protein is unstable. Note: this is a duplicated result from PMID: 23129764 The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 20334347, 21612213, 23129764, 36579626) PubMed:25524706 </p> <p>The C433R 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 </p> <p>The C433R protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 20334347, 23129764, 25524706, 36579626). PubMed:21612213 </p>
PP1_Strong			<p>23 segregations in 4 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 10819638, 16936947, 12671463), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family).</p>
PM2_Supporting			<p>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.</p>
PS4			<p>30 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 30484747, 10819638, 16936947, 12671463), which met PS4 (≥ 15 probands).</p>
PP3_Moderate			<p>The REVEL score = 0.913, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.</p>

Not Met criteria codes

BS1			<p>This criterion was not met as PM2_Supporting has been met.</p>
BS3			<p>This criterion was not met as PS3_Moderate has been met.</p>
BP7			<p>This is not an intronic, synonymous or non-coding variant.</p>

BP4			This criterion was not met as PP3 has been met.
PM5			PM5_Supporting could not be applied to this novel missense variant as although it did meet PP3, the Grantham score was lower (= 180) than the score for the different missense change at the same amino acid residue determined to be likely pathogenic by the ClinGen Glaucoma VCEP (c.1298G>A, p.Cys433Tyr, Grantham score = 194).
BA1			This criterion was not met as PM2_Supporting has been met.
PM4			This variant does not cause a protein length change.
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.

Curation History 		
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Showing 1 to 2 of 2 rows		
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