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Variant: NM_000261.2(MYOC):c.1440C>A (p.Asn480Lys)

Version: 2.0

CA119175

7951 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: d0adf58d-a397-461c-b1cd-9d3a527bd978
Approved on: 2026/1/13
Published on: 2026/1/12

HGVS expressions

NM_000261.2(MYOC):c.1440C>A (p.Asn480Lys)
NM_000261.2:c.1440C>A
NC_000001.11:g.171636000G>T
CM000663.2:g.171636000G>T
NC_000001.10:g.171605140G>T
CM000663.1:g.171605140G>T
NC_000001.9:g.169871763G>T
NG_008859.1:g.21634C>A
ENST00000037502.11:c.1440C>A
ENST00000637303.1:c.235-2630G>T
ENST00000638471.1:c.*778C>A
ENST00000037502.10:c.1440C>A
ENST00000614688.1:c.*404C>A
NM_000261.1:c.1440C>A

Pathogenic

Met criteria codes 6

PP1_Strong | PS3_Moderate | PS1 | PP3_Moderate | PM2_Supporting | PS4_Moderate

Not Met criteria codes 8

BA1 | PM5 | PM4 | BS1 | BS3 | PS2 | BP4 | BP7

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.1440C>A variant in MYOC is a missense variant predicted to cause substitution of Asparagine by Lysine at amino acid 480 (p.Asn480Lys). The highest minor allele frequency of this variant was in the Remaining genetic ancestry group of gnomAD (v4.1.0) = 0.000016 (1 allele out of 62,510), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.784, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC

function. The Asn480Lys protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs:16466712 and 35196929). 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, 16297911), however, the same level of evidence was not met. Over 100 segregations in 9 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 12107514, 24883016, 9556305, 36220364), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family). 14 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 22194650, 12872267, 12107514, 24883016, 9556305, 36220364, pers. comm. E Souzeau,), which met PS4_Moderate (≥ 6 probands). The same amino acid change (p.Asn480Lys), resulting from a different nucleotide change (c.1440C>G, ClinVarID: 1686785), was classified as pathogenic for JOAG (without the application of PS1) by the ClinGen Glaucoma VCEP and was not predicted to affect splicing, as assessed with SpliceAI (≤ 0.2), meeting the conditions for PS1 to apply. In summary, this variant met the criteria to receive a score of 15 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): PS1, PP1_Strong, PS3_Moderate, PS4_Moderate, PP3_Moderate, PM2_Supporting

Met criteria codes

PP1_Strong	✔	Over 100 segregations in 9 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 12107514, 24883016, 9556305, 36220364), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family).
PS3_Moderate	✔	The Asn480Lys protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs:16466712 and 35196929). 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, 16297911), however, the same level of evidence was not met.
PS1	✔	The same amino acid change (p.Asn480Lys), resulting from a different nucleotide change (c.1440C>G, ClinVarID: 1686785), was classified as pathogenic for JOAG (without the application of PS1) by the ClinGen Glaucoma VCEP and was not predicted to affect splicing, as assessed with SpliceAI (≤ 0.2), meeting the conditions for PS1 to apply.
PP3_Moderate	✔	The REVEL score = 0.784, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.
PM2_Supporting	✔	The highest minor allele frequency of this variant was in the Remaining genetic ancestry group of gnomAD (v4.1.0) = 0.000016 (1 allele out of 62,510), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles.
PS4_Moderate	✔	14 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 22194650, 12872267, 12107514, 24883016, 9556305, 36220364, pers comm. E Souzeau,), which met PS4_Moderate (≥ 6 probands).

Not Met criteria codes

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 variant does not cause a protein length change.

BS1		✖	This criterion was not met as PM2_Supporting has been met.
BS3		✖	This criterion was not met as PS3_Moderate has been met.
PS2		✖	This variant has not been identified de novo.
BP4		✖	This criterion was not met as PP3 has been met.
BP7		✖	This is not an intronic, synonymous or non-coding variant.

Curation History

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