Variant: NM_000261.2:c.976G>A

Version: 2.0

CA343725270

2442269 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7d3c820d-0e06-4153-94cf-0299999c3a75
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HGVS expressions

NM_000261.2:c.976G>A
NC_000001.11:g.171636464C>T
CM000663.2:g.171636464C>T
NC_000001.10:g.171605604C>T
CM000663.1:g.171605604C>T
NC_000001.9:g.169872227C>T
NG_008859.1:g.21170G>A
ENST00000037502.11:c.976G>A
ENST00000637303.1:c.235-2166C>T
ENST00000638471.1:c.*314G>A
ENST00000037502.10:c.976G>A
ENST00000614688.1:c.976G>A
NM_000261.1:c.976G>A

Uncertain Significance

Met criteria codes 4

PP1 PM2_Supporting BS3_Supporting PP3_Moderate

Not Met criteria codes 10

PM5 PM4 BS1 BP7 BP4 BA1 PS1 PS2 PS3 PS4

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.976G>A variant in MYOC is a missense variant predicted to cause substitution of Glycine by Serine at amino acid 326 (p.Gly326Ser). The highest minor allele frequency of this variant was in the Remaining genetic ancestry group of gnomAD (v4.1.0) = 0.00001600 (1 allele out of 62,504), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.869, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Gly326Ser protein had similar solubility and secretion levels to wild type myocilin protein in this study (PMID: 36267417). The assay met the

OddsPath threshold for BS3_Moderate (< 0.23), indicating that this variant did not impact protein function. 3 segregations in 1 family, with primary open angle glaucoma (POAG), have been reported (PMID: 22879734), which fulfilled PP1 (3-4 meioses). Only 1 proband with POAG had been reported (PMID: 22879734), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting. In summary, this variant met the criteria to receive a score of 2 and to be classified as a variant of uncertain significance (uncertain significance classification range -1 to 5, adapted from PMID: 32720330) for primary open angle glaucoma based on the ACMG/AMP criteria met, as specified by the ClinGen Glaucoma VCEP (v2.0.0, 5 Dec 2024): PP3_Moderate, BS3_Moderate, PP1, PM2_Supporting.

Met criteria codes

PP1	✔	3 segregations in 1 family, with primary open angle glaucoma (POAG), have been reported (PMID: 22879734), which fulfilled PP1 (3-4 meioses).
PM2_Supporting	✔	The highest minor allele frequency of this variant was in the Remaining genetic ancestry group of gnomAD (v4.1.0) = 0.00001600 (1 allele out of 62,504), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles.
BS3_Supporting	✔	applied at BS3_Moderate level: The Gly326Ser protein had similar solubility and secretion levels to wild type myocilin protein in this study (PMID: 36267417). The assay met the OddsPath threshold for BS3_Moderate (< 0.23), indicating that this variant did not impact protein function. The Gly326Ser protein is soluble and secreted. The assay in this study meets the OddsPath threshold for BS3_Moderate (< 0.23). PubMed:36267417
PP3_Moderate	✔	The REVEL score = 0.869, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.

Not Met criteria codes

PM5	✖	PM5 could not be applied to this variant as the other missense variant at this amino acid residue has a higher Grantham score.
PM4	✖	This criterion did not apply to this variant.
BS1	✖	This criterion was not met as PM2_Supporting has been met.
BP7	✖	This criterion did not apply to this variant.
BP4	✖	This criterion was not met as PP3 has been met.
BA1	✖	This criterion was not met as PM2_Supporting has been met.
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		✖	This criterion was not met as BS3_Moderate has been met.
PS4		✖	Only 1 proband with POAG had been reported (PMID: 22879734), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting.

Curation History

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