Variant: NM_000261.2(MYOC):c.1091G>T (p.Gly364Val)

Version: 2.0

CA119170

7947 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 30a3432f-835c-4e0b-942a-7a84d0c5f07c
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HGVS expressions

NM_000261.2:c.1091G>T
NM_000261.2(MYOC):c.1091G>T (p.Gly364Val)
NC_000001.11:g.171636349C>A
CM000663.2:g.171636349C>A
NC_000001.10:g.171605489C>A
CM000663.1:g.171605489C>A
NC_000001.9:g.169872112C>A
NG_008859.1:g.21285G>T
ENST00000037502.11:c.1091G>T
ENST00000637303.1:c.235-2281C>A
ENST00000638471.1:c.*429G>T
ENST00000037502.10:c.1091G>T
ENST00000614688.1:c.*55G>T
NM_000261.1:c.1091G>T

Pathogenic

Met criteria codes 5

PP1_Strong PP3_Moderate PS4_Supporting PS3_Moderate PM2_Supporting

Not Met criteria codes 9

BS1 BS3 BP4 BP7 PS1 PS2 BA1 PM5 PM4

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.1091G>T variant in MYOC is a missense variant predicted to cause substitution of Glycine by Valine at amino acid 364 (p.Gly364Val). 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 = 0.896, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Gly364Val protein had increased instability and reduced secretion levels compared to

wild type myocilin protein in these studies (PMIDs: 16466712, 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. 18 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 9535666), which fulfilled PP1_Strong (≥7 meioses in >1 family). 2 probands with JOAG or POAG have been reported carrying this variant (PMID: 10196380), 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, PS4_Supporting, PM2_Supporting.

Met criteria codes

PP1_Strong	✔	18 segregations in 2 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 9535666), which fulfilled PP1_Strong (≥7 meioses in >1 family).
PP3_Moderate	✔	The REVEL score = 0.896, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.
PS4_Supporting	✔	2 probands with JOAG or POAG have been reported carrying this variant (PMID: 10196380), which met PS4_Supporting (≥ 2 probands).
PS3_Moderate	✔	The Gly364Val protein had increased instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 16466712, 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. The Gly364Val 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 The Gly364Val protein is insoluble. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:15069026 The Gly364Val protein is unstable. Note: this is a duplicated result from PMID: 23129764 PubMed:25524706 The Gly364Val 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
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.

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_Moderate 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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