The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000261.2:c.1087G>A

Version: 2.0

CA343724770

1342962 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: f9eac996-1b82-4222-b685-e17c4c244c3d
Approved on: 2025/12/4
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HGVS expressions

NM_000261.2:c.1087G>A
NC_000001.11:g.171636353C>T
CM000663.2:g.171636353C>T
NC_000001.10:g.171605493C>T
CM000663.1:g.171605493C>T
NC_000001.9:g.169872116C>T
NG_008859.1:g.21281G>A
ENST00000037502.11:c.1087G>A
ENST00000637303.1:c.235-2277C>T
ENST00000638471.1:c.*425G>A
ENST00000037502.10:c.1087G>A
ENST00000614688.1:c.*51G>A
NM_000261.1:c.1087G>A

Likely Pathogenic

Met criteria codes 5

PP3_Moderate PM2_Supporting PP1_Moderate PS4_Supporting PS3_Moderate

Not Met criteria codes 9

PS1 PS2 PM5 PM4 BA1 BS1 BS3 BP7 BP4

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.1087G>A variant in MYOC is a missense variant predicted to cause substitution of Alanine by Threonine at amino acid 363 (p.Ala363Thr). 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 = 0.905, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function. The Ala363Thr protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in this study (J Hulleman pers. comm.). The assays met the OddsPath threshold for

PS3_Moderate (> 4.3) (when combined with PMID: 35196929), indicating that this variant did impact protein function. This protein has also been assessed in this other study (PMID: 14688426), however, the same level of evidence was not met. 5 segregations in 3 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 18334962, 16491872), which fulfilled PP1_Moderate (5-6 meioses). 4 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 15534471, 18334962), which met PS4_Supporting (≥ 2 probands). In summary, this variant met the criteria to receive a score of 8 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): PS3_Moderate, PP1_Moderate, PP3_Moderate, PS4_Supporting, PM2_Supporting

Met criteria codes

PP3_Moderate	✔	The REVEL score = 0.905, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on MYOC function.
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.
PP1_Moderate	✔	5 segregations in 3 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 18334962, 16491872), which fulfilled PP1_Moderate (5-6 meioses).
PS4_Supporting	✔	4 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 15534471, 18334962), which met PS4_Supporting (≥ 2 probands).
PS3_Moderate	✔	The Ala363Thr protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in this study (J Hulleman pers. comm.). The assays met the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMID: 35196929), indicating that this variant did impact protein function. This protein has also been assessed in this other study (PMID: 14688426), however, the same level of evidence was not met. The A363T protein is insoluble and has reduced secretion (J Hulleman pers. comm. unpublished data as part of the PMID:35196929 study). The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3). PubMed:35196929

Not Met criteria codes

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.
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.
BA1	✖	This criterion was not met as PM2_Supporting has been met.

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

Curation History

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