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.1138G>T

Version: 2.0

CA343724573

1342965 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 63fa2457-cd6f-4e00-8e40-a98b6cd33387
Approved on: 2026/1/13
Published on: 2026/1/12

HGVS expressions

NM_000261.2:c.1138G>T
NC_000001.11:g.171636302C>A
CM000663.2:g.171636302C>A
NC_000001.10:g.171605442C>A
CM000663.1:g.171605442C>A
NC_000001.9:g.169872065C>A
NG_008859.1:g.21332G>T
ENST00000037502.11:c.1138G>T
ENST00000637303.1:c.235-2328C>A
ENST00000638471.1:c.*476G>T
ENST00000037502.10:c.1138G>T
ENST00000614688.1:c.*102G>T
NM_000261.1:c.1138G>T

Likely Pathogenic

Met criteria codes 4

PP3_Strong PM5_Strong PM2_Supporting PS3_Moderate

Not Met criteria codes 10

PS1 PS2 PS4 PP1 PM4 BA1 BS1 BS3 BP7 BP4

Evidence Links 2

Expert Panel

Glaucoma VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Glaucoma Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MYOC Version 2.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Glaucoma VCEP

The c.1138G>T variant in MYOC is a missense variant predicted to cause substitution of Aspartic Acid by Tyrosine at amino acid 380 (p.Asp380Tyr). 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 = 0.964, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function. The Asp380Tyr 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. Only 1 proband with primary open angle glaucoma had been reported (PMID: 31302906), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting. Another missense variant (c.1139A>C, p.Asp380Ala, Grantham score (GS) = 126) in the same codon has been classified as pathogenic for juvenile open angle glaucoma (JOAG) by the ClinGen Glaucoma VCEP. Additionally, 2 other missense variants (c.1138G>C, p.Asp380His, GS = 81) and (c.1139A>G, p.Asp380Gly, GS = 94) have been classified as likely pathogenic for JOAG by the VCEP. The c.1138G>T, p.Asp380Tyr variant has a higher Grantham score (= 160) than the previously classified amino acid changes, was not predicted to affect splicing as assessed with SpliceAI (≤ 0.2), and met PP3, meeting the conditions for PM5_Strong to apply. 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 primary open angle glaucoma based on the ACMG/AMP criteria met, as specified by the ClinGen Glaucoma VCEP (v2.1.0, 2 October 2025): PM5_Strong, PP3_Strong, PS3_Moderate, PM2_Supporting (PP3 and PM5 capped at 5 points).

Met criteria codes

PP3_Strong	✔	The REVEL score = 0.964, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function.
PM5_Strong	✔	Another missense variant (c.1139A>C, p.Asp380Ala, Grantham score (GS) = 126) in the same codon has been classified as pathogenic for juvenile open angle glaucoma (JOAG) by the ClinGen Glaucoma VCEP. Additionally, 2 other missense variants (c.1138G>C, p.Asp380His, GS = 81) and (c.1139A>G, p.Asp380Gly, GS = 94) have been classified as likely pathogenic for JOAG by the VCEP. The c.1138G>T, p.Asp380Tyr variant has a higher Grantham score (= 160) than the previously classified amino acid changes, was not predicted to affect splicing as assessed with SpliceAI (≤ 0.2), and met PP3, meeting the conditions for PM5_Strong to apply.
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.
PS3_Moderate	✔	The Asp380Tyr 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. The D380Y 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 The D380Y protein is insoluble and has reduced secretion. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3). PubMed:36267417

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.
PS4	✖	Only 1 proband with primary open angle glaucoma had been reported (PMID: 31302906), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting.
PP1	✖	No segregations have been reported for this variant.

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

Showing 1 to 4 of 4 rows

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