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(MYOC):c.1138G>C (p.Asp380His)*

Version: 2.0

*CA119186*

*7961 (ClinVar)*

**Gene**: MYOC (HGNC:4653)
**Condition**: open-angle glaucoma (MONDO:0005338)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** b4a3436c-9253-4e58-a843-cc3eb040d0d0
**Approved on**: 2025/12/4
**Published on**: 2025/12/4

## *HGVS expressions*

**NM_000261.2(MYOC):c.1138G>C (p.Asp380His)**
**NM_000261.2:c.1138G>C**
NC_000001.11:g.171636302C>G
CM000663.2:g.171636302C>G
NC_000001.10:g.171605442C>G
CM000663.1:g.171605442C>G
NC_000001.9:g.169872065C>G
NG_008859.1:g.21332G>C
ENST00000037502.11:c.1138G>C
ENST00000637303.1:c.235-2328C>G
ENST00000638471.1:c.*476G>C
ENST00000037502.10:c.1138G>C
ENST00000614688.1:c.*102G>C
NM_000261.1:c.1138G>C

**Likely Pathogenic**

**Met criteria codes** 4

PP3_Strong PS3_Moderate PP1_Moderate PM2_Supporting

**Not Met criteria codes** 10

PM5 PM4 BA1 BS1 BS3 BP7 BP4 PS1 PS2 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.1138G>C variant in MYOC is a missense variant predicted to cause substitution of Aspartic Acid by Histidine at amino acid 380 (p.Asp380His). 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 = 0.965, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function. The Asp380His protein had increased insolubility and reduced secretion levels**

**compared to wild type myocilin protein in this study (PMID: 35196929). The assays met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function. 9 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 17499207), which fulfilled PP1_Moderate (≥ 5 meioses in ≥ 1 family, but not the ≥ 7 meioses in > 1 family for the strong criterion). Only 1 proband with JOAG had been reported (PMID: 17499207), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting. In summary, this variant met the criteria to receive a score of 9 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): PP3_Strong, PS3_Moderate, PP1_Moderate, PM2_Supporting**

### Met criteria codes

| | | |
|---|---|---|
| **PP3_Strong** | ✔ | The REVEL score = 0.965, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function. |
| **PS3_Moderate** | ✔ | The Asp380His protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in this study (PMID: 35196929). The assays met the OddsPath threshold for PS3_Moderate (> 4.3), indicating that this variant did impact protein function.<br><br>The D380H protein is not secreted and insoluble. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3). PubMed:35196929 |
| **PP1_Moderate** | ✔ | 9 segregations in 1 family, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMID: 17499207), which fulfilled PP1_Moderate (≥ 5 meioses in ≥ 1 family, but not the ≥ 7 meioses in > 1 family for the strong criterion). |
| **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

| | | |
|---|---|---|
| **PM5** | ✖ | PM5_Supporting could not be applied to this variant as the other missense variant with a lower Grantham score at the same amino acid residue (c.1138G>A, p.Asp380Asn, PMID: 12362081) was not classified as likely pathogenic or pathogenic and although it did meet PP3, the Grantham score was lower (= 81) than the score for the different missense change at the same amino acid residue determined to be pathogenic (without the application of PM5) by the ClinGen Glaucoma VCEP (c.1139A>C, p.Asp380Ala, Grantham score=126). This variant was used to apply PM5 to variants MYOC c.1139A>C, p.Asp380Ala and c.1139A>G, p.Asp380Gly which are located at the same amino acid residue. |
| **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. |
| **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 JOAG had been reported (PMID: 17499207), not meeting the ≥ 2 probands threshold required to meet PS4_Supporting. |

Curation History

Showing 1 to 3 of 3 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.