Variant: NM_000261.2:c.1139A>C

Version: 2.0

CA343724571

1342203 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9c3b9acb-015c-45ad-956e-7b10bbf078bd
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HGVS expressions

NM_000261.2:c.1139A>C
NC_000001.11:g.171636301T>G
CM000663.2:g.171636301T>G
NC_000001.10:g.171605441T>G
CM000663.1:g.171605441T>G
NC_000001.9:g.169872064T>G
NG_008859.1:g.21333A>C
ENST00000037502.11:c.1139A>C
ENST00000637303.1:c.235-2329T>G
ENST00000638471.1:c.*477A>C
ENST00000037502.10:c.1139A>C
ENST00000614688.1:c.*103A>C
NM_000261.1:c.1139A>C

Pathogenic

Met criteria codes 6

PM2_Supporting PP3_Strong PP1_Strong PM5 PS4_Moderate PS3_Moderate

Not Met criteria codes 8

BP7 BP4 PS1 PS2 PM4 BA1 BS1 BS3

Evidence Links 9

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.1139A>C variant in MYOC is a missense variant predicted to cause substitution of Aspartic Acid by Alanine at amino acid 380 (p.Asp380Ala). The highest minor allele frequency of this variant was in the European (non-Finnish) genetic ancestry group of gnomAD (v4.1.0) = 0.00000085 (1 allele out of 1,179,992), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles. The REVEL score = 0.97, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function. The Asp380Ala protein had increased insolubility, instability and reduced secretion levels compared to wild type myocilin protein

in these studies (PMIDs: 20334347, 21612213, 23129764, 16466712). 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: 15069026, 24333014), however, the same level of evidence was not met. 31 segregations in 6 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 17893668, 9863594, 9832047), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family). 7 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 17893668, 9863594, 9832047), which met PS4_Moderate (≥ 6 probands). Two other missense variants (c.1138G>C, p.Asp380His, Grantham score = 81, ClinVar ID: 7961 and c.1139A>G, p.Asp380Gly Grantham score = 94, ClinVar ID: 1342964) in the same codon have been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1139A>C, p.Asp380Ala variant has a higher Grantham score (= 126) 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 to apply. In summary, this variant met the criteria to receive a score of 14 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, PP3_Strong, PS3_Moderate, PS4_Moderate, PM5, PM2_Supporting (PP3 and PM5 capped at 5 points).

Met criteria codes

PM2_Supporting	✔	The highest minor allele frequency of this variant was in the European (non-Finnish) genetic ancestry group of gnomAD (v4.1.0) = 0.0000008 (1 allele out of 1,179,992), which met the ≤ 0.0001 threshold set for PM2_Supporting in a genetic ancestry group of at least 10,000 alleles.
PP3_Strong	✔	The REVEL score = 0.97, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on MYOC function.
PP1_Strong	✔	31 segregations in 6 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 17893668, 9863594, 9832047), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family).
PM5	✔	Two other missense variants (c.1138G>C, p.Asp380His, Grantham score = 81, ClinVar ID: 7961 and c.1139A>G, p.Asp380Gly Grantham score = 94, ClinVar ID: 1342964) in the same codon have been classified as likely pathogenic for juvenile open angle glaucoma by the ClinGen Glaucoma VCEP. The c.1139A>C, p.Asp380Ala variant has a higher Grantham score (= 126) 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 to apply. This variant would still be classified as pathogenic without the use of PM5 and was used to apply PM5 to variant MYOC c.1138G>T, p.Asp380Tyr which is located at the same amino acid residue.
PS4_Moderate	✔	7 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 17893668, 9863594, 9832047), which met PS4_Moderate (≥ 6 probands).
PS3_Moderate	✔	The Asp380Ala protein had increased insolubility, instability and reduced secretion levels compared to wild type myocilin protein in these studies (PMIDs: 20334347, 21612213, 23129764, 16466712). 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: 15069026, 24333014), however, the same level of evidence was not met. The D380A protein is unstable. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 21612213, 23129764, 25524706, 36579626). PubMed:20334347 The D380A 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 The D380A protein is unstable. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:24333014

The results for the D380A protein were indeterminate (partial solubility and secretion) and not included as evidence. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:16297911

The results for the D380A protein were indeterminate (partial solubility) and not included as evidence. The assay in this study meets the OddsPath threshold for PS3_Supporting (> 2.1) (when combined with PMID: 11004290) but not the threshold for PS3_Moderate (> 4.3). PubMed:10545602

The D380A 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 D380A protein is not secreted. The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3). PubMed:16466712

The D380A protein is unstable. Note: this is a duplicated result from PMID: 23129764 The assay in this study meets the OddsPath threshold for PS3_Moderate (> 4.3) (when combined with PMIDs: 20334347, 21612213, 23129764, 36579626) PubMed:25524706

The D380A protein is insoluble. The assay in this study does not meet the OddsPath threshold for PS3_Supporting (> 2.1). PubMed:15069026

Not Met criteria codes

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.
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.

Curation History

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