Variant: NM_000261.2(MYOC):c.1102C>T (p.Gln368Ter)

Version: 2.0

CA119172

7949 (ClinVar)

Gene: MYOC (HGNC:4653)
Condition: open-angle glaucoma (MONDO:0005338)
Inheritance Mode: Autosomal dominant inheritance
UUID: 399db6af-6807-459a-9953-39c259125cad
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HGVS expressions

NM_000261.2:c.1102C>T
NM_000261.2(MYOC):c.1102C>T (p.Gln368Ter)
NC_000001.11:g.171636338G>A
CM000663.2:g.171636338G>A
NC_000001.10:g.171605478G>A
CM000663.1:g.171605478G>A
NC_000001.9:g.169872101G>A
NG_008859.1:g.21296C>T
ENST00000037502.11:c.1102C>T
ENST00000637303.1:c.235-2292G>A
ENST00000638471.1:c.*440C>T
ENST00000037502.10:c.1102C>T
ENST00000614688.1:c.*66C>T
NM_000261.1:c.1102C>T

Pathogenic

Met criteria codes 4

PS4 PM4 PS3_Moderate PP1_Strong

Not Met criteria codes 11

PS1 PS2 PM5 PM2 BA1 PP3 PVS1 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.1102C>T variant in MYOC is predicted to cause a change in the length of the protein due to the insertion of a terminating codon instead of the usual Glutamine at amino acid 368 (p.Gln368Ter). This variant is predicted to cause a deletion of ≥ 10% of the protein within the conserved olfactomedin domain, meeting PM4. PVS1 did not apply, as the disease mechanism for MYOC variants associated with juvenile or primary open angle glaucoma (JOAG or POAG) is not loss-of-function. Although this variant had a minor allele frequency of

0.003296 in the European (Finnish) genetic ancestry group of gnomAD (v4.1.0, 211 alleles out of 64,018), which meets the ≥ 0.001 threshold for BS1, Gln368Ter is exempt from this criterion due to its incomplete penetrance and the presence of a common disease haplotype in all carriers. The Gln368Ter protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in this study (PMID: 16466712). The assay 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, 11004290, 11152659), however, the same level of evidence was not met. As this variant is exempt from the application of BS1, PP1 has been applied. 52 segregations in 10 families, with JOAG or POAG, have been reported (PMIDs: 11004290, 10815160, 11535458), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family). There were more family studies published than presented here. This variant is exempt from the rule which normally does not allow the application of PS4 unless PM2_Supporting is met. 23 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 11535458, 11004290, 10815160, 22736945, 11803488, 12189160), which met PS4 (≥15 probands). There were more probands published than presented here. In summary, this variant met the criteria to receive a score of 12 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): PS4, PP1_Strong, PM4, PS3_Moderate

Met criteria codes

PS4	✔	This variant is exempt from the rule which normally does not allow the application of PS4 unless PM2_Supporting is met. 23 probands with JOAG or POAG have been reported carrying this variant (PMIDs: 11535458, 11004290, 10815160, 22736945, 11803488, 12189160), which met PS4 (≥15 probands). There were more probands published than presented here.
PM4	✔	This truncating variant is predicted to cause a deletion of ≥ 10% of the protein and is within the conserved olfactomedin domain.
PS3_Moderate	✔	The Gln368Ter protein had increased insolubility and reduced secretion levels compared to wild type myocilin protein in this study (PMID: 16466712). The assay 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, 11004290, 11152659), however, the same level of evidence was not met. The Q368Ter protein is insoluble. The assay in this study meets the OddsPath threshold for PS3_Supporting (> 2.1) (when combined with PMID: 10545602) but not the threshold for PS3_Moderate (> 4.3). PubMed:11004290
PP1_Strong	✔	As this variant is exempt from the application of BS1, PP1 has been applied. 52 segregations in 10 families, with juvenile or primary open angle glaucoma (JOAG or POAG), have been reported (PMIDs: 11004290, 10815160, 11535458), which fulfilled PP1_Strong (≥ 7 meioses in > 1 family). There were more family studies published than presented here.

Not Met criteria codes

PS1	✖	This variant does not involve an amino acid change.
PS2	✖	This variant has not been identified de novo.
PM5	✖	This is not a missense variant.
PM2	✖	

The highest minor allele frequency of this variant was in the European (Finnish) genetic ancestry group of gnomAD (v4.1.0) = 0.003296 (211 alleles out of 64,018), which did not meet the ≤ 0.0001 threshold set for PM2_Supporting.

BA1	✖	This variant did not meet the ≥ 0.01 minor allele frequency threshold in gnomAD (v4.1.0).
PP3	✖	This criterion did not apply to this variant.
PVS1	✖	PVS1 did not apply, as the disease mechanism for MYOC variants associated with primary open angle glaucoma is not loss-of-function.
BS1	✖	Although this variant had a minor allele frequency of 0.003296 in the European (Finnish) genetic ancestry group of gnomAD (v4.1.0, 211 alleles out of 64,018), which meets the ≥ 0.001 threshold for BS1, Gln368Ter is exempt from this criterion due to its incomplete penetrance and the presence of a common disease haplotype in all carriers.
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 did not apply to this variant.

Curation History

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