Variant: NM_000104.4(CYP1B1):c.1168C>T (p.Arg390Cys)

Version: 1.0

CA1619847

335952 (ClinVar)

Gene: CYP1B1 (HGNC:1545)
Condition: CYP1B1-related glaucoma with or without anterior segment dysgenesis (MONDO:0800472)
Inheritance Mode: Autosomal recessive inheritance
UUID: fa79735c-c297-4c8a-916b-78990d57b9e9
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HGVS expressions

NM_000104.4:c.1168C>T
NM_000104.4(CYP1B1):c.1168C>T (p.Arg390Cys)
NC_000002.12:g.38071186G>A
CM000664.2:g.38071186G>A
NC_000002.11:g.38298329G>A
CM000664.1:g.38298329G>A
NC_000002.10:g.38151833G>A
NG_008386.2:g.9916C>T
ENST00000490576.2:c.1168C>T
ENST00000610745.5:c.1168C>T
ENST00000492443.1:n.546C>T
ENST00000494864.1:c.55C>T
ENST00000610745.4:c.1168C>T
ENST00000613082.1:n.563C>T
ENST00000614273.1:c.1168C>T
NM_000104.3:c.1168C>T

Pathogenic

Met criteria codes 5

PP1_Strong | PM5_Strong | PP3_Strong | PM2_Supporting | PM3_Very Strong

Not Met criteria codes 11

PS1 | PS2 | PS3 | PM1 | PM4 | PVS1 | BA1 | BS1 | BS4 | BP7 | BP4

Evidence Links 0

Expert Panel

Glaucoma VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Glaucoma Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CYP1B1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Glaucoma VCEP

The c.1168C>T variant in CYP1B1 is a missense variant predicted to cause substitution of Arginine by Cysteine at amino acid 390 (p.Arg390Cys). The highest minor allele frequency of this variant was in the Remaining genetic ancestry group of gnomAD (v4.1.0) =

0.00006402 (4 alleles out of 62,484), which met the ≤ 0.0005 threshold set for PM2_Supporting in a genetic ancestry group of at least 2,000 alleles. The REVEL score = 0.965, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on CYP1B1 function. There was no functional evidence predicting a damaging or benign impact of this variant on CYP1B1 function. 3 affected segregations with a CYP1B1-related phenotype have been reported (PMIDs: 21081970), which fulfilled PP1_Strong. There were more family studies published than presented here. This variant has been identified in five individuals with a CYP1B1-related phenotype. Three of these individuals are compound heterozygous for the variant and a pathogenic or likely pathogenic variant (confirmed in trans) (PMIDs: 23218701, 38755526, 21081970). Two individuals are homozygous (non-consanguineous) for the variant (PMID: 14507861). Total proband points = 4, meeting PM3_Very strong. There were more cases published than presented here. Two other missense variants (p.Arg390His, Grantham score = 29, ClinVar ID: 592512 and p.Arg390Ser, Grantham score = 110, ClinVar ID: 2203048) in the same codon have been classified as pathogenic for a CYP1B1-related phenotype by the ClinGen Glaucoma VCEP. CYP1B1:p.Arg390Cys has a higher Grantham score (= 180) 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 18 and to be classified as pathogenic (pathogenic classification ≥ 10, adapted from PMID: 32720330) for CYP1B1-related glaucoma with or without anterior segment dysgenesis (ASD) based on the ACMG/AMP criteria met, as specified by the ClinGen Glaucoma VCEP (v1.0, 06.11.2025): PM3_Very Strong, PM5_Strong, PP1_Strong, PP3_Strong, PM2_Supporting (combination of PP3 and PM5 is capped at 5 points).

Met criteria codes

PP1_Strong	✔	3 affected segregations with a CYP1B1-related phenotype have been reported (PMIDs: 21081970), which fulfilled PP1_Strong. There were more family studies published than presented here.
PM5_Strong	✔	Two other missense variants (p.Arg390His, Grantham score = 29, ClinVar ID: 592512 and p.Arg390Ser, Grantham score = 110, ClinVar ID: 2203048) in the same codon have been classified as pathogenic for a CYP1B1-related phenotype by the ClinGen Glaucoma VCEP. CYP1B1:p.Arg390Cys has a higher Grantham score (= 180) 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.
PP3_Strong	✔	The REVEL score = 0.965, which met the ≥ 0.932 threshold for PP3_Strong, predicting a damaging effect on CYP1B1 function.
PM2_Supporting	✔	The highest minor allele frequency of this variant was in the Remaining genetic ancestry group of gnomAD (v4.1.0) = 0.00006402 (4 alleles out of 62,484), which met the ≤ 0.0005 threshold set for PM2_Supporting in a genetic ancestry group of at least 2,000 alleles.
PM3_Very Strong	✔	This variant has been identified in five individuals with a CYP1B1-related phenotype. Three of these individuals are compound heterozygous for the variant and a pathogenic or likely pathogenic variant (confirmed in trans) (PMIDs: 23218701, 38755526, 21081970). Two individuals are homozygous (non-consanguineous) for the variant (PMID: 14507861). Total proband points = 4, meeting PM3_Very strong. There were more cases published than presented here.

Not Met criteria codes

PS1	✖	An established likely pathogenic or pathogenic variant causing the same amino acid change has not been identified.
PS2	✖	This variant has not been identified de novo.

PS3		✖	No functional evidence has been found for this variant.
PM1		✖	This missense variant is located outside well-established functional domains.
PM4		✖	This criterion did not apply to this variant.
PVS1		✖	This criterion did not apply to this variant.
BA1		✖	This criterion was not met as PM2_Supporting has been met.
BS1		✖	This criterion was not met as PM2_Supporting has been met.
BS4		✖	Non-segregation involving this variant has not been reported.
BP7		✖	This criterion did not apply to this variant.
BP4		✖	This criterion was not met as PP3 has been met.

Curation History

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