Variant: NM_000104.4(CYP1B1):c.431A>G (p.Gln144Arg)

Version: 1.0

CA1620036

1329081 (ClinVar)

Gene: CYP1B1 (HGNC:1545)
Condition: CYP1B1-related glaucoma with or without anterior segment dysgenesis (MONDO:0800472)
Inheritance Mode: Autosomal recessive inheritance
UUID: f5eaacff-9204-432f-905a-41b83607f51d
Approved on: 2025-11-19
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HGVS expressions

NM_000104.4:c.431A>G
NM_000104.4(CYP1B1):c.431A>G (p.Gln144Arg)
NC_000002.12:g.38074958T>C
CM000664.2:g.38074958T>C
NC_000002.11:g.38302101T>C
CM000664.1:g.38302101T>C
NC_000002.10:g.38155605T>C
NG_008386.2:g.6144A>G
ENST00000490576.2:c.431A>G
ENST00000610745.5:c.431A>G
ENST00000494864.1:c.-70-3648A>G
ENST00000610745.4:c.431A>G
ENST00000613082.1:n.376-550A>G
ENST00000614273.1:c.431A>G
NM_000104.3:c.431A>G

Uncertain Significance

Met criteria codes 1

PM2_Supporting

Not Met criteria codes 15

BA1 PP1 PP3 PM1 PM3 PM5 PM4 PVS1 BS1 BS4 BP4 BP7 PS1 PS2 PS3

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 CYP1B1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Glaucoma VCEP

The c.431A>G variant in CYP1B1 is a missense variant predicted to cause substitution of Glutamine by Arginine at amino acid 144 (p.Gln144Arg). The highest minor allele frequency of this variant was in the South Asian genetic ancestry group of gnomAD (v4.1) = 0.0003193 (28 alleles out of 87702), which met the ≤ 0.0005 threshold set for PM2_Supporting in a genetic ancestry group of at least

2,000 alleles. This missense variant was not predicted to affect splicing, as assessed with SpliceAI (≤ 0.1), and the REVEL score = 0.445, which was neither above nor below the thresholds for PP3 (≥ 0.644) or BP4 (≤ 0.290), predicting a damaging or benign impact on CYP1B1 function. PS3_Supporting was not applied as the assays reported did not meet the OddsPath threshold (> 2.1) or the threshold for abnormal impact on protein function in the assay could not be determined (PMID: 27243976). This variant has not been identified as homozygous or compound heterozygous with one other variant. One affected individual carries the Gln144Arg variant but they also carry two other CYP1B1 variants (Phe156Cys and His413_I414delinsGlnLys, both VUS), phase unknown. This person is excluded from assessing PM3 as the causative variant cannot be determined. In summary, this variant met the criteria to receive a score of 1 and to be classified as a variant of uncertain significance (uncertain significance classification range -1 to 5, 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): PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	The highest minor allele frequency of this variant was in the South Asian genetic ancestry group of gnomAD (v4.1) = 0.0003193 (28 alleles out of 87702), which met the ≤ 0.0005 threshold set for PM2_Supporting in a genetic ancestry group of at least 2,000 alleles.

Not Met criteria codes

BA1	✖	This criterion was not met as PM2_Supporting has been met.
PP1	✖	No segregations have been reported for this variant.
PP3	✖	This missense variant was not predicted to affect splicing, as assessed with SpliceAI (≤ 0.1), and it had a REVEL score = 0.445, which did not meet the ≥ 0.644 threshold required for PP3.
PM1	✖	This missense variant is located outside well-established functional domains.
PM3	✖	This variant has not been identified as homozygous or compound heterozygous with one other variant. One affected individual carries the Gln144Arg variant but they also carry two other CYP1B1 variants (Phe156Cys and His413_I414delinsGlnLys, both VUS), phase unknown. This person is excluded from assessing PM3 as the causative variant cannot be determined.
PM5	✖	PM5 did not apply to this variant at any strength as it did not meet PP3.
PM4	✖	This criterion did not apply to this variant.
PVS1	✖	This criterion did not apply to this variant.
BS1	✖	This criterion was not met as PM2_Supporting has been met.
BS4	✖	Non-segregation involving this variant has not been reported.
BP4	✖	

Although this missense variant was not predicted to affect splicing, as assessed with SpliceAI (≤ 0.1), it had a REVEL score = 0.445, which did not meet the ≤ 0.290 threshold required for BP4.

BP7	✖	This criterion did not apply to this variant.
PS1	✖	An established likely pathogenic or pathogenic variant causing this same amino acid change has not been identified.
PS2	✖	This variant has not been identified de novo.
PS3	✖	PS3_Supporting was not applied as the assays reported did not meet the OddsPath threshold (> 2.1) or the threshold for abnormal impact on protein function in the assay could not be determined (PMID: 27243976). Did not meet the OddsPath threshold for PS3_Supporting (> 2.1) or unable to determine threshold for abnormal impact on protein function in the assay. PubMed:27243976

Curation History

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