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Variant: NM_000104.4(CYP1B1):c.182G>A (p.Gly61Glu)

Version: 1.0

CA254237

7730 (ClinVar)

Gene: CYP1B1 (HGNC:1545)
Condition: CYP1B1-related glaucoma with or without anterior segment dysgenesis (MONDO:0800472)
Inheritance Mode: Autosomal recessive inheritance
UUID: e590fca4-0674-4996-8eaf-ad5cd2c49e4b
Approved on: 2025-11-19
Published on: 2025-11-18

HGVS expressions

NM_000104.4:c.182G>A
NM_000104.4(CYP1B1):c.182G>A (p.Gly61Glu)
NC_000002.12:g.38075207C>T
CM000664.2:g.38075207C>T
NC_000002.11:g.38302350C>T
CM000664.1:g.38302350C>T
NC_000002.10:g.38155854C>T
NG_008386.2:g.5895G>A
ENST00000490576.2:c.182G>A
ENST00000610745.5:c.182G>A
ENST00000490576.1:c.182G>A
ENST00000494864.1:c.-70-3897G>A
ENST00000610745.4:c.182G>A
ENST00000613082.1:n.375+573G>A
ENST00000614273.1:c.182G>A
NM_000104.3:c.182G>A

Pathogenic

Met criteria codes 5

PM3_Very Strong | PP1_Strong | PM1 | PS3_Supporting | PP3_Moderate

Not Met criteria codes 11

BA1 | BS1 | BS4 | BP7 | BP4 | PS1 | PS2 | PVS1 | PM2 | PM5 | PM4

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.182G>A variant in CYP1B1 is a missense variant predicted to cause substitution of Glycine by Glutamic acid at amino acid 61 (p.Gly61Glu). This missense variant is located in the hinge region, meeting PM1. The highest minor allele frequency of this variant was in

the Middle Eastern genetic ancestry group of gnomAD (v4.1.0) = 0.006305 (33 alleles out of 5234), which did not meet the PM2_Supporting allele frequency threshold (≤ 0.0005) or the BS1 allele frequency threshold (≥ 0.01). The REVEL score = 0.795, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on CYP1B1 function. A previous study (PMID: 18470941) demonstrated that the Gly61Glu protein had reduced 17B Estradiol Activity levels compared to wild type CYP1B1 protein and another study (PMID: 12807732) demonstrated that the protein had reduced Benzo[a]pyrene Activity levels compared to wild type CYP1B1 protein. Both studies met the OddsPath threshold for PS3_Supporting (> 2.1), indicating that this variant did impact protein function. This variant was also assessed in PMIDs: 11740343, 19793111, 19234632, 27243976, however 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. 3 affected segregations with a CYP1B1-related phenotype have been reported (PMID: 9497261), which fulfilled PP1_Strong. There were more family studies published than presented here. This variant has been identified in eight individuals with a CYP1B1-related phenotype. Five individuals are compound heterozygous for the variant and a pathogenic or likely pathogenic variant (1 confirmed in trans and 4 phase unknown). Three individuals are homozygous (2 consanguineous and 1 non-consanguineous) for the variant (PMIDs: 9497261, 12372064, 16490498, 19234632, 22128238, 30270463). Total points = 4, meeting PM3_Very strong. There were more cases published than presented here. In summary, this variant met the criteria to receive a score of 17 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, PP1_Strong, PM1, PP3_Moderate, PS3_Supporting.

Met criteria codes

PM3_Very Strong	✔	This variant has been identified in eight individuals with a CYP1B1-related phenotype. Five individuals are compound heterozygous for the variant and a pathogenic or likely pathogenic variant (1 confirmed in trans and 4 phase unknown). Three individuals are homozygous (2 consanguineous and 1 non-consanguineous) for the variant (PMIDs: 9497261, 12372064, 16490498, 19234632, 22128238, 30270463). Total points = 4, meeting PM3_Very strong. There were more cases published than presented here.
PP1_Strong	✔	3 affected segregations with a CYP1B1-related phenotype have been reported (PMID: 9497261), which fulfilled PP1_Strong. There were more family studies published than presented here.
PM1	✔	This missense variant is located in the hinge region, meeting PM1.
PS3_Supporting	✔	A previous study (PMID: 18470941) demonstrated that the Gly61Glu protein had reduced 17B Estradiol Activity levels compared to wild type CYP1B1 protein and another study (PMID: 12807732) demonstrated that the protein had reduced Benzo[a]pyrene Activity levels compared to wild type CYP1B1 protein. Both studies met the OddsPath threshold for PS3_Supporting (> 2.1), indicating that this variant did impact protein function. This variant was also assessed in PMIDs: 11740343, 19793111, 19234632, 27243976, however 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.
PP3_Moderate	✔	The REVEL score = 0.795, which was within the 0.773-0.931 range for PP3_Moderate, predicting a damaging effect on CYP1B1 function.

Not Met criteria codes

BA1	✖	This variant did not meet the ≥ 0.05 minor allele frequency threshold in gnomAD (v4.1).
BS1	✖	The highest minor allele frequency of this variant was in the Middle Eastern genetic ancestry group of gnomAD (v4.1) = 0.006305 (33 alleles out of 5234), which did not meet the ≥ 0.01 threshold set for BS1.

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.
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.
PVS1		✖	This criterion did not apply to this variant.
PM2		✖	The highest minor allele frequency of this variant was in the Middle Eastern genetic ancestry group of gnomAD (v4.1) = 0.006305 (33 alleles out of 5234), which did not meet the ≤ 0.0005 threshold set for PM2_Supporting.
PM5		✖	No other likely pathogenic or pathogenic missense variant at this amino acid residue has been identified.
PM4		✖	This criterion did not apply to this variant.

Curation History

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