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Variant: NM_000350.3(ABCA4):c.2453G>A (p.Gly818Glu)

Version: 1.0

CA227000

99135 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 327b9089-3b49-41fc-8429-03397507a82a
Approved on: 2025/12/5
Published on: 2025/12/19

HGVS expressions

NM_000350.3:c.2453G>A
NM_000350.3(ABCA4):c.2453G>A (p.Gly818Glu)
NC_000001.11:g.94055245C>T
CM000663.2:g.94055245C>T
NC_000001.10:g.94520801C>T
CM000663.1:g.94520801C>T
NC_000001.9:g.94293389C>T
NG_009073.1:g.70905G>A
ENST00000370225.4:c.2453G>A
ENST00000649773.1:c.2231G>A
ENST00000370225.3:c.2453G>A
ENST00000536513.5:c.-65+7929G>A
NM_000350.2:c.2453G>A

Pathogenic

Met criteria codes 5

PM3 PP3_Moderate PS4 PS3_Supporting PM2_Supporting

Not Met criteria codes 1

PP4

Evidence Links 0

Expert Panel

ABCA4 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen ABCA4 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCA4 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

ABCA4 VCEP

The NM_000350.3(ABCA4):c.2453G>A variant in ABCA4 is a missense variant predicted to cause substitution of glycine by glutamic acid at amino acid 818 (p.Gly818Glu). The total minor allele frequency in gnomAD v4.1.0 is 0.00004151 (67/1614030 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.937 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls with an OR = 12.7 and the CI is 5.89-27.63, which

is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629). This variant has been detected in multiple individuals with ABCA4-related retinopathy. Of those individuals, 1 was compound heterozygous for the variant and a pathogenic variant ([A1038V;L541P]) that was not confirmed in trans (PMID: 19074458), and another individual was homozygous for the variant (PM3; PMID: 23419329). ABCA4 expression in HEK293 cells showed a reduction to 40%-52% of wild-type ABCA4 and ATPase activity was 63 ± 5% compared to wild-type indicating that this variant impacts protein function (PS3_Supporting; PMID:33375396). In summary, this variant meets the criteria to be classified as pathogenic for ABCA4-related retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen ABCA4 VCEP (Specification Version 1.0): PS4, PM3, PP3_Moderate, PM2_Supporting, PS3_Supporting.

Met criteria codes

PM3	✔	This variant has been detected in at least 2 individuals with ABCA4-related retinopathy. Of those individuals, 1 was compound heterozygous for the variant and a pathogenic variant ([A1038V;L541P]) which was not confirmed in trans (PM3= 0.5 points; PMID: 19074458). One individual was homozygous for the variant (PM3= 0.5 points; PM3; PMID: 23419329).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.937 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 12.7 and the CI is 5.89-27.63, which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629).
PS3_Supporting	✔	ABCA4 expression in HEK293 cells showed a reduction to 40%-52% of wild-type ABCA4 and ATPase activity was 63 ± 5% compared to wild-type indicating that this variant impacts protein function (PS3_Supporting; PMID:33375396).
PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.00004151 (67/1614030 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PP4	✖	This variant is found in many cases of ABCA4-related retinopathy, but none meet the ABCA4 VCEP criteria to apply PP4 (PMIDs: 24317291, 24695063, 37296172, 30718709, 28099317, 29925512, 28446513, 19074458, 23419329; ClinVar SCVs: SCV001241100.1, SCV000511886.4, SCV002521204.1, SCV000926780.2).

Curation History

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