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Variant: NM_000350.3(ABCA4):c.1957C>T (p.Arg653Cys)

Version: 1.0

CA226965

99108 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: b3a28565-2982-4450-8485-f54aae931472
Approved on: 2025/10/28
Published on: 2025/11/14

HGVS expressions

NM_000350.3:c.1957C>T
NM_000350.3(ABCA4):c.1957C>T (p.Arg653Cys)
NC_000001.11:g.94060740G>A
CM000663.2:g.94060740G>A
NC_000001.10:g.94526296G>A
CM000663.1:g.94526296G>A
NC_000001.9:g.94298884G>A
NG_009073.1:g.65410C>T
ENST00000370225.4:c.1957C>T
ENST00000649773.1:c.1957C>T
ENST00000370225.3:c.1957C>T
ENST00000472033.1:n.77C>T
ENST00000536513.5:c.-65+2434C>T
NM_000350.2:c.1957C>T

Pathogenic

Met criteria codes 5

PM2_Supporting PS3_Supporting PM3 PS4 PP3_Moderate

Evidence Links 1

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:c.1957C>T variant in ABCA4 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 653 (p.Arg653Cys). The total minor allele frequency in gnomAD v4.1.0 is 0.00002666 (43/1612644 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.852 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. The OR is 139.4 and the CI is 43.93-707.41, 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 at least 4 individuals with ABCA4-related retinopathy. Of those individuals, 2 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant unconfirmed in trans (c.3386G>T; p.(Arg1129Leu)(PM3; PMID:35119454). ATPase activity in HEK293 cells showed reduction by over 20% 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 1.0.0): PS4, PP3_Moderate, PM3, PM2_Supporting, PS3_Supporting.

Met criteria codes

PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.00002666 (43/1612644 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PS3_Supporting	✔	ATPase activity in HEK293 cells showed reduction by over 20% compared to wild type indicating that this variant impacts protein function (PS3_Supporting; PMID:33375396). Figure 8B shows ATPase activity of this variant to be reduced by over 20% compared to wild type PubMed:33375396
PM3	✔	This variant has been detected in at least 4 individuals with ABCA4-related retinopathy. Of those individuals, 2 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant unconfirmed in trans (c.3386G>T;p.(Arg1129Leu)- 1 point)(PM3; PMID:35119454).
PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 139.4 and the CI is 43.93- 707.41, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1 (PS4; PMID: 35120629).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.852 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).

Curation History

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