

Variant: *NM_000350.3(ABCA4):c.1958G>A (p.Arg653His)*

Version: 1.0

CA958377 [↗](#)

417982 (ClinVar) [↗](#)

Gene: ABCA4 ([HGNC:24](#))

Condition: ABCA4-related retinopathy ([MONDO:0800406](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: d9a8e9ab-2e1d-4ee3-80e2-ff2cc33041d7

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HGVS expressions

NM_000350.3(ABCA4):c.1958G>A (p.Arg653His)

NM_000350.3:c.1958G>A

NC_000001.11:g.94060739C>T

CM000663.2:g.94060739C>T

NC_000001.10:g.94526295C>T

CM000663.1:g.94526295C>T

NC_000001.9:g.94298883C>T

NG_009073.1:g.65411G>A

ENST00000370225.4:c.1958G>A

ENST00000649773.1:c.1958G>A

ENST00000370225.3:c.1958G>A

ENST00000472033.1:n.78G>A

ENST00000536513.5:c.-65+2435G>A

NM_000350.2:c.1958G>A

Pathogenic

Met criteria codes **6**

PS4

PM2_Supporting

PP3_Moderate

PM3

PM5

BS3_Supporting

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.1958G>A variant in ABCA4 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 653 (p.Arg653His). The total minor allele frequency in gnomAD v4.1.0 is 0.00001488 (24/1612788 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.889 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 32.8 and the CI is 9.71- 141.13, 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 3 individuals with ABCA4-related retinopathy. Of those individuals, one individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant which was confirmed in trans by parental/family testing (PM3; PMID:23776498). Another missense variant, c.1957C>T; p.Arg653Cys, in the same codon has been classified as pathogenic for ABCA4-related retinopathy by the ClinGen ABCA4 VCEP (PM5). ATPase activity in HEK293 cells showed ATPase activity similar to and above 80% of wildtype ABCA4 indicating that this variant does not impact protein function (BS3_Supporting; PMID:33375396). In summary, this variant meets the criteria to be classified as pathogenic for ABCA4-related retinopathy. Although there are both pathogenic and benign types of evidence for this variant, the pathogenic evidence points [11pts -1pt (BS3_S) = 10 pts] are still consistent with a pathogenic classification. ACMG/AMP criteria applied, as specified by the ClinGen ABCA4 VCEP (Specification Version 1.0.0): PS4, PP3_Moderate, PM3, PM5, PM2_Supporting, BS3_Supporting.

Met criteria codes

PS4			The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 32.8 and the CI is 9.71- 141.13, which is above the ABCA4 VCEP threshold of ≥ 5 , where the CI does not contain 1 (PS4; PMID: 35120629).
PM2_Supporting			The total minor allele frequency in gnomAD v4.1.0 is 0.00001488 (24/1612788 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PP3_Moderate			The computational predictor REVEL gives a score of 0.889 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PM3			This variant has been detected in at least 3 individuals with ABCA4-related retinopathy. Of those individuals, one individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant which was confirmed in trans by parental/family testing (c.4604dup, 1 point) (PM3; PMID:23776498).
PM5			Another missense variant, c.1957C>T (p.Arg653Cys)(ClinVarID:99108), in the same codon has been classified as pathogenic for ABCA4-related retinopathy by the ClinGen ABCA4 VCEP, and Splice AI revealed no expected effects on splicing (PM5).
BS3_Supporting			ATPase activity in HEK293 cells showed ATPase activity similar to and above 80% of wildtype ABCA4 indicating that this variant does not impact protein function (BS3_Supporting; PMID:33375396).
Figure 8B shows similar ATPase activity to WT and ATPase activity >80% of wildtype PubMed:33375396 			

Curation History 

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