

Variant: *NM_000350.3(ABCA4):c.6415C>T (p.Arg2139Trp)*

Version: 1.0

CA227402 [↗](#)

99458 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0da4793f-a666-4f88-acd4-147615b10c1d

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HGVS expressions

NM_000350.3(ABCA4):c.6415C>T (p.Arg2139Trp)

NM_000350.3:c.6415C>T

NC_000001.11:g.94000900G>A

CM000663.2:g.94000900G>A

NC_000001.10:g.94466456G>A

CM000663.1:g.94466456G>A

NC_000001.9:g.94239044G>A

NG_009073.1:g.125250C>T

ENST00000370225.4:c.6415C>T

ENST00000370225.3:c.6415C>T

ENST00000536513.5:c.2791C>T

NM_000350.2:c.6415C>T

Pathogenic

Met criteria codes **4**

PS4

PP3_Moderate

PM3_Strong

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.6415C>T variant in ABCA4 is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 2139 (p.Arg2139Trp). The total minor allele frequency in gnomAD v4.1.0 is 0.00001115 (18/1614184 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.975 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 of 35.7 and the CI is 2.87-1852.51, 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 who were all compound heterozygous for the variant and a pathogenic variant (c.5018+2T>C, c.2345G>A; p.Trp782Ter), c.3994C>T; p.Gln1332Ter) with 1 of those was confirmed in trans by family testing (PM3_Strong; PMIDs: 37498587, 38602673). 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_Strong, PM2_Supporting, PP3_Moderate.

Met criteria codes

PS4			The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 35.7 and the CI is 2.87-1852.51, 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 0.975 which is above the threshold of >0.772 , evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PM3_Strong			This variant has been detected in at least 3 individuals with ABCA4-related retinopathy. Of those individuals, all 3 were compound heterozygous for the variant and a pathogenic variant (c.5018+2T>C; c.2345G>A (p.Trp782Ter); c.3994C>T (p.Gln1332Ter)) and 1 of those was confirmed in trans by family testing (PM3= 2 points; PM3_Strong; PMIDs: 37498587, 38602673).
PM2_Supporting			The total minor allele frequency in gnomAD v4.1.0 is 0.00001115 (18/1614184 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 has been found in at least 4 probands with ABCA4-related retinopathy, but none meet the phenotype criteria specified by the ABCA4 VCEP to apply PP4.
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Curation History

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