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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
Approved on: 2025/12/5
Published on: 2025/12/19

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

PM2_Supporting PS4 PM3_Strong PP3_Moderate

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

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).
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).
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).
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).

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.

Curation History

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