The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000350.3(ABCA4):c.6416G>C (p.Arg2139Pro)

Version: 1.0

CA10611614

298222 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3732d6a3-cfc5-41c3-826d-de2e784c2b6e
Approved on: 2025/12/5
Published on: 2025/12/19

HGVS expressions

NM_000350.3:c.6416G>C
NM_000350.3(ABCA4):c.6416G>C (p.Arg2139Pro)
NC_000001.11:g.94000899C>G
CM000663.2:g.94000899C>G
NC_000001.10:g.94466455C>G
CM000663.1:g.94466455C>G
NC_000001.9:g.94239043C>G
NG_009073.1:g.125251G>C
ENST00000370225.4:c.6416G>C
ENST00000370225.3:c.6416G>C
ENST00000536513.5:c.2792G>C
NM_000350.2:c.6416G>C

Pathogenic

Met criteria codes 6

PM3 PM5 PP3_Moderate PS4 PP1 PM2_Supporting

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.6416G>C variant in ABCA4 is a missense variant predicted to cause substitution of arginine by proline at amino acid 2139 (p.Arg2139Pro). The total minor allele frequency in gnomAD v4.1.0 is 0.000006195 (10/1614076 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.997 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 is infinity and the CI is 2.24-infinity, 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 1 individual with ABCA4-related retinopathy who was compound heterozygous for the variant and a pathogenic variant (c.2588G>C; p.Gly863Ala) which was confirmed in trans by parental/family testing (PMID: 28559085; PM3). The variant has been reported to segregate with ABCA4-related retinopathy in the proband and 1 similarly affected relative (PP1; PMID: 25472526). Another missense variant, c.6415C>T (p.Arg2139Trp), 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). 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): PS4, PM3, PP1, PM2_Supporting, PP3_Moderate, PM5.

Met criteria codes

PM3	✔	This variant has been detected in at least 1 individual with ABCA4-related retinopathy. This individual was compound heterozygous for the variant and a pathogenic variant (c.2588G>C p.Gly863Ala) which was confirmed in trans by parental/family testing (PM3= 1 point; PMID: 28559085; PM3).
PM5	✔	Another missense variant, c.6415C>T (p.Arg2139Trp), 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). c.6416G>A (p.Arg2139Gln) used the current variant for PM5, so not scoring here to avoid circular logic.
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.997 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 infinity and the CI is 2.24-infinity, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1 (PS4; PMID: 35120629).
PP1	✔	The variant has been reported to segregate with ABCA4-related retinopathy in the proband and 1 similarly affected relative (PP1; PMID: 25472526).
PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.000006195 (10/1614076 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.