

Variant: NM_000350.3(ABCA4):c.6445C>T (p.Arg2149Ter)

Version: 1.0

CA227404 [↗](#)

99460 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 2a28d610-baee-43f6-9eef-6d2f37a33593

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HGVS expressions

NM_000350.3(ABCA4):c.6445C>T (p.Arg2149Ter)

NM_000350.3:c.6445C>T

NC_000001.11:g.94000870G>A

CM000663.2:g.94000870G>A

NC_000001.10:g.94466426G>A

CM000663.1:g.94466426G>A

NC_000001.9:g.94239014G>A

NG_009073.1:g.125280C>T

ENST00000370225.4:c.6445C>T

ENST00000370225.3:c.6445C>T

ENST00000536513.5:c.2821C>T

NM_000350.2:c.6445C>T

Pathogenic

Met criteria codes **4**

PVS1

PS4

PM2_Supporting

PM3_Supporting

Not Met criteria codes **1**

BS1

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:c.6445C>T (p.Arg2149Ter) variant in ABCA4 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 47 out of 50 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The total minor allele frequency in gnomAD v4.1.0 is 0.000006196 (10/1614050 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls with and OR of 86.3 and the CI is 30.40-338.60, 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 who was

homozygous for the variant (PMID: 36284460; PM3_Supporting). 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: PVS1, PS4, PM3_Supporting, PM2_Supporting.

Met criteria codes

PVS1			This is a nonsense variant located in exon 47 out of 50, and introduces a premature stop codon between codons 1-2255 (PVS1).
PS4			The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 86.3 and the CI is 30.40-338.60, which is above the ABCA4 VCEP threshold of >3, where the CI does not contain 1 (PS4; PMID: 35120629).
PM2_Supporting			The total minor allele frequency in gnomAD v4.1.0 is 0.000006196 (10/1614050 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PM3_Supporting			This variant has been detected in at least 1 individual with ABCA4-related retinopathy. This individual was homozygous for the variant (PM3= 0.5points, PMID: 36284460; PM3_Supporting).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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Curation History



 

 

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