

Variant: *NM_000350.3(ABCA4):c.4720G>T (p.Glu1574Ter)*

Version: 1.0

CA341283936 [↗](#)

1460063 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 79085d1c-e389-46f8-845b-60475b80fdd3

Approved on: 2025/12/5

Published on: 2025/12/23

HGVS expressions

NM_000350.3(ABCA4):c.4720G>T (p.Glu1574Ter)

NM_000350.3:c.4720G>T

NC_000001.11:g.94021899C>A

CM000663.2:g.94021899C>A

NC_000001.10:g.94487455C>A

CM000663.1:g.94487455C>A

NC_000001.9:g.94260043C>A

NG_009073.1:g.104251G>T

ENST00000370225.4:c.4720G>T

ENST00000370225.3:c.4720G>T

ENST00000460514.1:n.214G>T

ENST00000536513.5:c.1096G>T

NM_000350.2:c.4720G>T

Pathogenic

Met criteria codes **4**

PS4

PP4

PM2_Supporting

PVS1

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.4720G>T (p.Glu1574Ter) variant in ABCA4 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 33 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 0.000003420 (5/1461888 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. The OR is infinity and the CI is (10.92-infinity), which is above the ABCA4 VCEP threshold of >5,

where the CI does not contain 1 (PS4; PMID: 35120629). At least two probands met phenotypic criteria for ABCA4-related retinopathy (PP4, PMIDs: 32619608, 31674661). 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, PP4, PM2_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 infinity and the CI is (10.92-infinity), which is above the ABCA4 VCEP threshold of >3, where the CI does not contain 1 (PS4; PMID: 35120629).
PP4			At least two patients with this variant displayed orange-yellow flecks in the retina, decreased peripheral vision, decreased central visual acuity, night blindness, macular atrophy, and age of onset before with 2 or more ABCA4 variants found by WES, which is highly specific for ABCA4-related retinopathy (PP4, PMIDs: 32619608, 31674661).
PM2_Supporting			The total minor allele frequency in gnomAD v4.1.0 is 0.000003420 (5/1461888 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PVS1			This is a nonsense variant located in exon 33 out of 50, and introduces a premature stop codon between codons 1-2255 (PVS1).

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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