

Variant: *NM_000350.3(ABCA4):c.1519G>T (p.Asp507Tyr)*

Version: 1.0

CA958508 [↗](#)

2733942 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0d5777bd-1f3e-4a30-812b-ed62aa6342b9

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HGVS expressions

NM_000350.3:c.1519G>T

NM_000350.3(ABCA4):c.1519G>T (p.Asp507Tyr)

NC_000001.11:g.94077725C>A

CM000663.2:g.94077725C>A

NC_000001.10:g.94543281C>A

CM000663.1:g.94543281C>A

NC_000001.9:g.94315869C>A

NG_009073.1:g.48425G>T

ENST00000370225.4:c.1519G>T

ENST00000649773.1:c.1519G>T

ENST00000370225.3:c.1519G>T

NM_000350.2:c.1519G>T

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP3_Moderate

PS4

PP1

PM3_Strong

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.1519G>T variant in ABCA4 is a missense variant predicted to cause substitution of aspartic acid by tyrosine at amino acid 507 (p.Asp507Tyr). The total minor allele frequency in gnomAD v4.1.0 is 0.000007436 (12/1613864 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.832 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 4 individuals with ABCA4-related retinopathy who were compound heterozygous for the variant and a pathogenic variant (c.6416G>C; p.Arg2139Pro, c.3208_3209insGT, c.3210_3211dup, c.4139C>T; p.Pro1380Leu) and none of those were confirmed in trans (PM3_Strong; PMIDs: 25472526, 23982839, 37705246; LOVD entry). The variant has been reported to segregate with ABCA4-related retinopathy in the proband and 1 similarly affected relative (PP1; PMID: 25472526). 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_Strong, PM2_Supporting, PP1, PP3_Moderate.

Met criteria codes

PM2_Supporting			The total minor allele frequency in gnomAD v4.1.0 is 0.000007436 (12/1613864 alleles), which is lower than the ClinGen ABCA4 VCEP’s threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PP3_Moderate			The computational predictor REVEL gives a score of 0.832 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 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).
PP1			The variant has been reported to segregate with ABCA4-related retinopathy in the proband and 1 similarly affected relative (PP1; PMID: 25472526).
PM3_Strong			This variant has been detected in at least 4 individuals with ABCA4-related retinopathy. Of those individuals, all 4 were compound heterozygous for the variant and a pathogenic variant (c.6416G>C p.(Arg2139Pro); c.3208_3209insGT; c.3210_3211dup; c.4139C>T (p.Pro1380Leu)) and none of those were confirmed in trans (PM3= 2 points; PM3_Strong; PMIDs: 25472526, 23982839, 37705246; LOVD entry).

Not Met criteria codes

PP4			This variant is present in at least 9 individuals with ABCA4-related retinopathy, but none meet the PP4 criteria specified by the ABCA4 VCEP.
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Curation History



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