

Variant: *NM_000350.3:c.4793C>A*

Version: 1.0

CA227239 [↗](#)

99321 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 399dfd75-c421-4659-9305-1b953c22709b

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HGVS expressions

NM_000350.3:c.4793C>A

NC_000001.11:g.94021695G>T

CM000663.2:g.94021695G>T

NC_000001.10:g.94487251G>T

CM000663.1:g.94487251G>T

NC_000001.9:g.94259839G>T

NG_009073.1:g.104455C>A

ENST00000370225.4:c.4793C>A

ENST00000370225.3:c.4793C>A

ENST00000460514.1:n.287C>A

ENST00000536513.5:c.1169C>A

NM_000350.2:c.4793C>A

Pathogenic

Met criteria codes **6**

PM2_Supporting

PP3

PP4

PS3_Supporting

PS4

PM3_Strong

Evidence Links **1**

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

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

ABCA4 VCEP

The NM_000350.3:c.4793C>A variant is a missense variant predicted to cause this substitution of alanine to aspartic acid at amino acid 1598 (p.Ala1598Asp). The total minor allele frequency in gnomAD v4.1.1 is 0.00002046 (<0.0001) which is lower than the threshold for PM2_Supporting. The computational predictor REVEL gives a score of 0.685 which is in the range of 0.644-0.772, evidence that predicts a damaging effect on ABCA4 function (PP3). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls with an OR of 187.4 and CI of 60.33 to 933.94, 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 three individuals with ABCA4-related retinopathy. At least

one patient with this variant displayed presence of at least two ABCA4 variants, onset under 18 years of age, reduced central vision bilaterally and on the presence of “dark choroid” sign of fluorescein angiography, and scotomas, which is highly specific for ABCA4-related retinopathy (PP4, PMID: 27014590). Two were compound heterozygous for the variant and a pathogenic variant and one of those was confirmed in trans by parental testing, and one individual was homozygous for the variant (PM3_Strong; PMIDs: 27014590, 34874912, 41677386). ABCA4 expression and ATPase activity in HEK293 cells showed significant reduction of more than 20% compared to wildtype, indicating that this variant impacts protein function (PS3_Supporting; PMID: 32845050). In summary, this variant meets the criteria to be classified as pathogenic for ABCA4-related retinopathy, specifically when co-occurring with other disease-causing ABCA4 variants, based on the ACMG/AMP criteria applied, as specified by the ClinGen ABCA4 VCEP (Specification Version 1.0): PS4, PM3_Strong, PP4, PP3, PS3_Supporting, PM2_Supporting.

Met criteria codes

PM2_Supporting			The total minor allele frequency in gnomAD v4.1.1 is 0.00002046 (33/1613150 alleles), which is lower than the ClinGen ABCA4 VCEP’s threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PP3			The computational predictor REVEL gives a score of 0.685 which is in the range of 0.644-0.772, evidence that predicts a damaging effect on ABCA4 function (PP3).
PP4			At least one patient with this variant displayed presence of at least two ABCA4 variants, onset under 18 years of age, reduced central vision bilaterally and on the presence of “dark choroid” sign of fluorescein angiography, and scotomas, which is highly specific for ABCA4-related retinopathy (PP4, PMID: 27014590).
PS3_Supporting			ABCA4 expression and ATPase activity in HEK293 cells showed significant reduction of more than 20% compared to wildtype, indicating that this variant impacts protein function (PS3_Supporting; PMID: 32845050). Transfected HEK293T cells with variant showed Relative Expression 0.64±0.19. Relative ATPase Activity ATPase–ATR 0.48±0.21. Relative ATPase Activity ATPase+ATR 0.32±0.12 compared to wildtype. (Table 1) PubMed:32845050 
PS4			The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 187.4 and the CI is 60.33 to 933.94, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1 (PS4; PMID: 35120629).
PM3_Strong			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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