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Variant: NM_000350.3(ABCA4):c.6289C>T (p.Pro2097Ser)

Version: 1.0

CA341277622

2202780 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3397c7be-1a0e-4d35-93ec-2d0e9e1fedf9
Approved on: 2026/2/24
Published on: 2026/2/27

HGVS expressions

NM_000350.3(ABCA4):c.6289C>T (p.Pro2097Ser)
NM_000350.3:c.6289C>T
NC_000001.11:g.94001099G>A
CM000663.2:g.94001099G>A
NC_000001.10:g.94466655G>A
CM000663.1:g.94466655G>A
NC_000001.9:g.94239243G>A
NG_009073.1:g.125051C>T
ENST00000370225.4:c.6289C>T
ENST00000370225.3:c.6289C>T
ENST00000536513.5:c.2665C>T
NM_000350.2:c.6289C>T

Pathogenic

Met criteria codes 5

PM3 PP3_Moderate PS4 PP4 PM2_Supporting

Not Met criteria codes 3

PM5 BS1 BP4

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.6289C>T variant in ABCA4 is a missense variant predicted to cause substitution of proline by serine at amino acid 2097 (p.Pro2097Ser). The total minor allele frequency in gnomAD v4.1.0 is 0.000001239 (2/1613554 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.926 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. The OR is infinity and the CI is 14.02-infinity, which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629). At least one patient with this variant

displayed age of onset under 18 years of age, macular flecks, two ABCA4 variants found on WES, and decreased central visual acuity, which is highly specific for ABCA4-related retinopathy (PP4; PMID: 31674661). This variant has been detected in at least 2 individuals with ABCA4-related retinopathy. Of those individuals, 2 were compound heterozygous for the variant and a pathogenic variant, c.4720G>T p.(Glu1574*) and c.4605_4606insT (p.Lys1536Ter), which was not confirmed in trans (PM3; PMIDs: 31674661, 25474345). 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 1.0.0): PS4, PM3, PP4, PM2_Supporting, PP3_Moderate.

Met criteria codes

PM3	✔	This variant has been detected in at least 2 individuals with ABCA4-related retinopathy. Of those individuals, 2 were compound heterozygous for the variant and a pathogenic variant, c.4720G>T p.(Glu1574*) and c.4605_4606insT (p.Lys1536Ter), which was not confirmed in trans (PM3=1 point; PMIDs: 31674661, 25474345; PM3).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.926 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 14.02-infinity, which is above the ABCA4 VCEP threshold of >3, where the CI does not contain 1 (PS4; PMID: 35120629).
PP4	✔	At least one patient with this variant displayed age of onset under 18 years of age, macular flecks, 2 ABCA4 variants found on WES, and decreased central visual acuity, which is highly specific for ABCA4-related retinopathy (PP4, PMID: 31674661).
PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.000001239 (2/1613554 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5	✖	Another missense variant, c.6290C>T (p.Pro2097Leu), in the same codon has been classified as likely pathogenic for ABCA4-related retinopathy by the ClinGen ABCA4 VCEP, and Splice AI revealed no expected effects on splicing. However, the other variant met a LP classification using PM5 for this variant, so to avoid circular logic, the current variant will not have PM5 applied.
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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