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Variant: NM_000350.3(ABCA4):c.6722T>C (p.Leu2241Pro)

Version: 1.0

CA341276236

836905 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: f7ce81c1-92ef-4705-be22-1a4ee3a042f9
Approved on: 2025/12/5
Published on: 2025/12/19

HGVS expressions

NM_000350.3(ABCA4):c.6722T>C (p.Leu2241Pro)
NM_000350.3:c.6722T>C
NC_000001.11:g.93997868A>G
CM000663.2:g.93997868A>G
NC_000001.10:g.94463424A>G
CM000663.1:g.94463424A>G
NC_000001.9:g.94236012A>G
NG_009073.1:g.128282T>C
ENST00000370225.4:c.6722T>C
ENST00000370225.3:c.6722T>C
ENST00000536513.5:c.3098T>C
NM_000350.2:c.6722T>C

Pathogenic

Met criteria codes 5

PP4 PM3_Strong PP3_Moderate PS4 PM2_Supporting

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.6722T>C variant in ABCA4 is a missense variant predicted to cause substitution of leucine by proline at amino acid 2441 (p.Leu2241Pro). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The odds ratio is infinity and the confidence interval is 2.24 to infinity, which is above the ABCA4 VCEP threshold of >5, where the confidence interval does not contain 1 (PS4; PMID: 35120629). The computational predictor REVEL gives a score of 0.869 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate). At least one proband meets the ABCA4-related retinopathy phenotype criteria (PP4, PMID: 30563929).

This variant has been detected in at least two individuals with ABCA4-related retinopathy who were compound heterozygous for the variant and a pathogenic variant, as confirmed in trans by NGS and Sanger sequencing (PM3_Strong, PMID: 33261146). 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): PM3_Strong, PS4, PP3_Moderate, PP4, PM2_Supporting.

Met criteria codes

PP4	✔	At least one patient with this variant displayed presence of at least two ABCA4 variants, onset under 18 years of age, beaten-bronze appearance, pigment mottling, poor visual acuity, macular atrophy, and yellowish flecks in maculae, which is highly specific for ABCA4-related retinopathy (PP4_Supporting, PMID: 30563929)
PM3_Strong	✔	This variant has been detected in at least two individuals with ABCA4-related retinopathy who were compound heterozygous for the variant and a pathogenic variant, as confirmed in trans by NGS and Sanger sequencing (PM3_Strong, PMID: 33261146).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.869 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 2.24 to infinity, which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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