

Variant: NM_000350.3(ABCA4):c.4457C>T (p.Pro1486Leu)

Version: 1.0

CA227192 [↗](#)

99283 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 99cef40a-cd37-4a13-bec4-6b893231e171

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HGVS expressions

NM_000350.3(ABCA4):c.4457C>T (p.Pro1486Leu)

NM_000350.3:c.4457C>T

NC_000001.11:g.94029527G>A

CM000663.2:g.94029527G>A

NC_000001.10:g.94495083G>A

CM000663.1:g.94495083G>A

NC_000001.9:g.94267671G>A

NG_009073.1:g.96623C>T

ENST00000370225.4:c.4457C>T

ENST00000370225.3:c.4457C>T

ENST00000536513.5:c.833C>T

NM_000350.2:c.4457C>T

Pathogenic

Met criteria codes **5**

PP3_Moderate

PM2_Supporting

PP4

PS4

PM3

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.4457C>T variant in ABCA4 is a missense variant predicted to cause substitution of proline by leucine at amino acid 1486 (p.Pro1486Leu). The total minor allele frequency in gnomAD v4.1.0 is 0.00003787 (61/1610682 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.88 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 58.8 and the CI is (30.38-124.55), which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629). At least one proband meeting

phenotypic criteria for ABCA4-related retinopathy (PP4, PMID:33841504). This variant has been detected in at least 4 individuals with ABCA4-related retinopathy who were homozygous for the variant (PM3; PMID: 32619608, 32036094). 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): PS4, PM3, PP3_Moderate, PP4, PM2_Supporting.

Met criteria codes

PP3_Moderate			The computational predictor REVEL gives a score of 0.88 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PM2_Supporting			The total minor allele frequency in gnomAD v4.1.0 is 0.00003787 (61/1610682 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PP4			At least one patient with this variant displayed presence of at least two ABCA4 variants, onset under 18 years of age, macular flecks on imaging, decreased central visual acuity, and macular atrophy, which is highly specific for ABCA4-related retinopathy (PP4, PMID:33841504).
PS4			The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 58.8 and the CI is (30.38-124.55), which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629).
PM3			This variant has been detected in at least 4 individuals with ABCA4-related retinopathy. Four individuals were homozygous for the variant (PM3= 1 point; PM3; PMID: 32619608, 32036094).

Curation History



 

 

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