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Variant: NM_000350.3(ABCA4):c.3386G>T (p.Arg1129Leu)

Version: 1.0

CA227116

99224 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3ec3094e-c85d-4ca9-8e11-9092ed4543f5
Approved on: 2025/12/5
Published on: 2025/12/19

HGVS expressions

NM_000350.3(ABCA4):c.3386G>T (p.Arg1129Leu)
NM_000350.3:c.3386G>T
NC_000001.11:g.94041345C>A
CM000663.2:g.94041345C>A
NC_000001.10:g.94506901C>A
CM000663.1:g.94506901C>A
NC_000001.9:g.94279489C>A
NG_009073.1:g.84805G>T
ENST00000370225.4:c.3386G>T
ENST00000370225.3:c.3386G>T
ENST00000536513.5:c.-64-1256G>T
NM_000350.2:c.3386G>T

Pathogenic

Met criteria codes 3

PS4 PM3_Strong PP3_Moderate

Not Met criteria codes 2

PM2 BS1

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.3386G>T variant in ABCA4 is a missense variant predicted to cause substitution of arginine by leucine at amino acid 1129 (p.Arg1129Leu). The computational predictor REVEL gives a score of 0.848 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 82.6 and the CI is 57.49 to 122.45, which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629). This variant is reported to be a founder variant in Spanish patients with ABCA4-related retinopathy, accounting for 24% of the disease-associated alleles in the cohort (PMID: 16917483). Of those

individuals, five were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and two of those were confirmed in trans by parental testing. Five individuals were homozygous for the variant (PM3_Strong, PMID:16917483). 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): PM3_Strong, PS4, PP3_Moderate.

Met criteria codes

PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 82.6 and the CI is 57.49 to 122.45, which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629).
PM3_Strong	✔	This variant has been detected in at least 5 individuals with ABCA4-related retinopathy. Of those individuals, one was compound heterozygous for the variant and a pathogenic variant, confirmed in trans by parental testing. Four individuals were homozygous for the variant (PM3 = 2 points, PM3_Strong, PMID:16917483).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.848 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate). Splice AI is 0.02.

Not Met criteria codes

PM2	✖	The total minor allele frequency in gnomAD v4.1.0 is 0.0001016 (164/1614062 alleles), and the GroupMax filtering allele frequency is 0.001295. This is higher than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), and lower than the threshold for BS1_Supporting (>0.00163). Therefore, none of the population data codes are met.
BS1	✖	The total minor allele frequency in gnomAD v4.1.0 is 0.0001016 (164/1614062 alleles), and the GroupMax filtering allele frequency is 0.001295. This is higher than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), and lower than the threshold for BS1_Supporting (>0.00163). Therefore, none of the population data codes are met.

Curation History

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