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Variant: NM_000350.3(ABCA4):c.4577C>T (p.Thr1526Met)

Version: 1.0

CA227218

99303 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 13fe40f1-8c93-430c-98f7-a728b8447031
Approved on: 2025/12/5
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HGVS expressions

NM_000350.3(ABCA4):c.4577C>T (p.Thr1526Met)
NM_000350.3:c.4577C>T
NC_000001.11:g.94025011G>A
CM000663.2:g.94025011G>A
NC_000001.10:g.94490567G>A
CM000663.1:g.94490567G>A
NC_000001.9:g.94263155G>A
NG_009073.1:g.101139C>T
ENST00000370225.4:c.4577C>T
ENST00000370225.3:c.4577C>T
ENST00000460514.1:n.71C>T
ENST00000536513.5:c.953C>T
NM_000350.2:c.4577C>T

Pathogenic

Met criteria codes 4

PS4 PP3_Moderate PP1 PM3_Strong

Not Met criteria codes 3

PM2 BA1 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.4577C>T variant in ABCA4 is a missense variant predicted to cause substitution of threonine by methionine at amino acid 1526 (p.Thr1526Met). The computational predictor REVEL gives a score of 0.887 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 with an OR = 80.9 and the CI is 43.88 to 163.71, 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 two individuals

with ABCA4-related retinopathy that were compound heterozygous for the variant and a pathogenic variant, confirmed in trans by NGS, Sanger, whole-exome parallel sequencing, and/or segregation analysis (PM3_Strong, PMID: 35344533 and 36672815). The variant has been reported to segregate with ABCA4-related retinopathy in 1 affected proband and 1 relative within a single family (PP1; PMID: 35344533). 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_Strong, PP3_Moderate, PP1_Supporting.

Met criteria codes

PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 80.9 and the CI is 43.88 to 163.71, which is above the ABCA4 VCEP threshold of >3, where the CI does not contain 1 (PS4; PMID: 35120629).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.887 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PP1	✔	The variant has been reported to segregate with ABCA4-related retinopathy in 1 affected proband and 1 relative within a single family (PP1_Supporting; PMID: 35344533).
PM3_Strong	✔	This variant has been detected in two individuals with ABCA4-related retinopathy. Of those individuals, two were compound heterozygous for the variant and a pathogenic variant, confirmed in trans by NGS, Sanger, whole-exome parallel sequencing, and segregation analysis (PM3_Strong, PMID: 35344533 and 36672815)

Not Met criteria codes

PM2	✖	The total minor allele frequency in gnomAD v4.1.0 is 0.0001227 (198/1614058 alleles), and the GroupMax filtering allele frequency is 0.0001358. 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.
BA1	✖	The GroupMax filtering allele frequency in gnomAD v4.1.0 is 0.0001358, which is lower than the ClinGen ABCA4 VCEP's threshold for BA1 (>0.163), therefore, this criterion is not met (BA1 not met).
BS1	✖	The total minor allele frequency in gnomAD v4.1.0 is 0.0001227 (198/1614058 alleles), and the GroupMax filtering allele frequency is 0.0001358. 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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