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Variant: NM_000350.3(ABCA4):c.4139C>T (p.Pro1380Leu)

Version: 1.0

CA129033

7904 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0beaa673-7ced-40db-89b2-207cf995608d
Approved on: 2025/12/5
Published on: 2025/12/19

HGVS expressions

NM_000350.3:c.4139C>T
NM_000350.3(ABCA4):c.4139C>T (p.Pro1380Leu)
NC_000001.11:g.94031110G>A
CM000663.2:g.94031110G>A
NC_000001.10:g.94496666G>A
CM000663.1:g.94496666G>A
NC_000001.9:g.94269254G>A
NG_009073.1:g.95040C>T
ENST00000370225.4:c.4139C>T
ENST00000370225.3:c.4139C>T
ENST00000536513.5:c.515C>T
NM_000350.2:c.4139C>T

Pathogenic

Met criteria codes 5

PM3 PP1_Moderate PP3_Moderate PS4 PP4

Not Met criteria codes 4

PM2 BA1 BS1 PS3

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.4139C>T variant in ABCA4 is a missense variant predicted to cause substitution of proline by leucine at amino acid 1380 (p.Pro1380Leu). The computational predictor REVEL gives a score of 0.867 which is above the threshold of >0.772 meeting PP3_Moderate. The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls with an OR = 114.7 and the CI is 76.81-177.05, 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 2 individuals with ABCA4-related retinopathy. At least one reported proband with this variant met criteria for the ABCA4-related retinopathy phenotype (PP4; PMID: 10396622). Both individuals were homozygous for

the variant (PM3; PMIDs: 19074458, 18854780). The variant has been reported to segregate with ABCA4-related retinopathy in 3 affected meioses across more than 1 family (PP1_Moderate; PMIDs: 10396622, 19074458). 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): PP4, PS4, PM3, PP1_Moderate, PP3_Moderate.

Met criteria codes

PM3	✔	This variant has been detected in at least 2 individuals with ABCA4-related retinopathy. Both individuals were homozygous for the variant (PM3= 1 point; PM3; PMIDs: 19074458, 18854780).
PP1_Moderate	✔	The variant has been reported to segregate with ABCA4-related retinopathy in 3 affected meioses across more than 1 family (PP1_Moderate; PMIDs: 10396622, 19074458).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.867 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 114.7 and the CI is 76.81-177.05, which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629).
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: 10396622).

Not Met criteria codes

PM2	✖	The total minor allele frequency in gnomAD v4.1.0 is 0.0002887 (466/1613962 alleles), and the GroupMax filtering allele frequency is 0.0002798. 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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	The total minor allele frequency in gnomAD v4.1.0 is 0.0002887 (466/1613962 alleles), and the GroupMax filtering allele frequency is 0.0002798. 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.
PS3	✖	Expression in HEK 293 cells showed a reduction compared to wild-type. However, this assay does not meet the requirements for use of PS3 by the ClinGen ABCA4 VCEP.

Curation History

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