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Variant: NM_000350.3(ABCA4):c.6410G>A (p.Cys2137Tyr)

Version: 1.0

CA341277358

2202779 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 82dbe751-d28d-4af4-913e-063b9c0b025d
Approved on: 2026/2/24
Published on: 2026/2/27

HGVS expressions

NM_000350.3(ABCA4):c.6410G>A (p.Cys2137Tyr)
NM_000350.3:c.6410G>A
NC_000001.11:g.94000905C>T
CM000663.2:g.94000905C>T
NC_000001.10:g.94466461C>T
CM000663.1:g.94466461C>T
NC_000001.9:g.94239049C>T
NG_009073.1:g.125245G>A
ENST00000370225.4:c.6410G>A
ENST00000370225.3:c.6410G>A
ENST00000536513.5:c.2786G>A
NM_000350.2:c.6410G>A

Pathogenic

Met criteria codes 6

PM2_Supporting PP4 PS3_Supporting PS4 PP3_Moderate PM3_Supporting

Not Met criteria codes 2

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.6410G>A variant is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 2137 (p.Cys2137Tyr). The total minor allele frequency in gnomAD v4.1.0 is 0.000000684 (1/1461892 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.967 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 infinity and the CI is 25.35-infinity, which is above the ABCA4 VCEP threshold of >5, where the CI does not contain 1 (PS4; PMID: 35120629). At least one patient with this variant

displayed flecks in the retina on fundus images, decreased visual acuity, night blindness, was under 18 years of age, and had two ABCA4 variants found by NGS, which is highly specific for ABCA4-related retinopathy (PP4; PMID: 32619608). This variant has been detected in at least 1 homozygous individual with ABCA4-related retinopathy (PM3_Supporting; PMID: 19959634). ABCA4 expression and ATPase activity in HEK293 cells both showed a decrease compared to WT, with a F-Index of 0, indicating that this variant impacts protein function (PS3_Supporting; PMID: 32845050). 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): PS4, PP4, PM3_Supporting, PP3_Moderate, PM2_Supporting, PS3_Supporting.

Met criteria codes

PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.000000684 (1/1461892 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 flecks in the retina on fundus images, decreased visual acuity, night blindness, was under 18 years of age, and had 2 ABCA4 variants found by NGS, which is highly specific for ABCA4-related retinopathy (PP4, PMID: 32619608).
PS3_Supporting	✔	ABCA4 expression and ATPase activity in HEK293 cells both showed a decrease compared to WT, with a F-Index of 0, indicating that this variant impacts protein function (PS3_Supporting; PMID: 32845050).
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 25.35-infinity, 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 0.967 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PM3_Supporting	✔	This variant has been detected in at least 1 individual with ABCA4-related retinopathy. This individual was homozygous for the variant (0.5 points, PMID: 19959634; PM3_Supporting).

Not Met criteria codes

BA1	✖	This code is not applicable at this time due to the presence of several known common hypomorphic alleles that have a higher MAF.
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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