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Variant: NM_000350.3(ABCA4):c.6383A>G (p.His2128Arg)

Version: 1.0

CA227399

99455 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: 657da4d7-4173-4950-9d25-b65c68a86632
Approved on: 2025/12/5
Published on: 2025/12/19

HGVS expressions

NM_000350.3:c.6383A>G
NM_000350.3(ABCA4):c.6383A>G (p.His2128Arg)
NC_000001.11:g.94001005T>C
CM000663.2:g.94001005T>C
NC_000001.10:g.94466561T>C
CM000663.1:g.94466561T>C
NC_000001.9:g.94239149T>C
NG_009073.1:g.125145A>G
ENST00000370225.4:c.6383A>G
ENST00000370225.3:c.6383A>G
ENST00000536513.5:c.2759A>G
NM_000350.2:c.6383A>G

Pathogenic

Met criteria codes 4

PM2_Supporting PS4 PM3_Strong PP3_Moderate

Not Met criteria codes 2

PP4 BP4

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.6383A>G variant in ABCA4 is a missense variant predicted to cause substitution of histidine by arginine at amino acid 2128 (p. His2128Arg). This variant is found in many cases of ABCA4-related retinopathy, but none meet the ClinGen ABCA4 VCEP criteria to apply PP4 (PMIDs: 23419329, 29925512, 25474345, 11328725, 10206579, 37217489, 37648803). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 47.7 and the CI is 4.71-2311.43, 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 5 individuals with ABCA4-related retinopathy. Of those individuals, all were compound heterozygous for the variant

and a pathogenic variant (c.3G>T (p.Met1Ile); c.4457C>T (p.Pro1486Leu); c.5882G>A (p.Gly1961Glu); c.2588G>C p.Gly863Ala; c.2453G>A (p.Gly818Glu)) and none of those were confirmed in trans (PM3_Strong; PMIDs: 37648803, 37217489, 25474345, 29925512, 23419329). The total minor allele frequency in gnomAD v4.1.0 is 0.000001239 (2/1614076 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.974 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate). 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, PM3_Strong, PM2_Supporting, PP3_Moderate.

Met criteria codes

PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.000001239 (2/1614076 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 47.7 and the CI is 4.71-2311.43, which is above the ABCA4 VCEP threshold of >3, 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, all were compound heterozygous for the variant and a pathogenic variant (c.3G>T (p.Met1Ile); c.4457C>T (p.Pro1486Leu); c.5882G>A (p.Gly1961Glu); c.2588G>C p.Gly863Ala; c.2453G>A (p.Gly818Glu)) and none of those were confirmed in trans (PM3=2.5 points; PM3_Strong; PMIDs: 37648803, 37217489, 25474345, 29925512, 23419329).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.974 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).

Not Met criteria codes

PP4	✖	This variant is found in many cases of ABCA4-related retinopathy, but none meet to ABCA4 VCEP criteria to apply PP4 (PMIDs: 23419329, 29925512, 25474345, 11328725, 10206579, 37217489, 37648803).
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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