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Variant: NM_000350.3(ABCA4):c.3323G>A (p.Arg1108His)

Version: 1.0

CA227109

99219 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: e569ecbd-fd02-4e05-a822-a3bfdc013474
Approved on: 2026/3/24
Published on: 2026/3/28

HGVS expressions

NM_000350.3(ABCA4):c.3323G>A (p.Arg1108His)
NM_000350.3:c.3323G>A
NC_000001.11:g.94042766C>T
CM000663.2:g.94042766C>T
NC_000001.10:g.94508322C>T
CM000663.1:g.94508322C>T
NC_000001.9:g.94280910C>T
NG_009073.1:g.83384G>A
ENST00000370225.4:c.3323G>A
ENST00000370225.3:c.3323G>A
ENST00000536513.5:c.-64-2677G>A
NM_000350.2:c.3323G>A

Pathogenic

Met criteria codes 5

PS4 PP3_Moderate PM3 PM5 PM2_Supporting

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.3323G>A variant in ABCA4 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 1108; p.Arg1108His. The total minor allele frequency in gnomAD v4.1.0 is 0.0000465 (75/1614058 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.843 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function meeting PP3_Moderate. The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls with an OR of 87.3 and CI of 26.27-456.18, 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 multiple individuals with ABCA4-related retinopathy. Of those individuals, three were compound heterozygous with a pathogenic or likely pathogenic variant but none were confirmed in trans (c.6416G>C;p.Arg2139Pro, [c.2588G>C;5603A>T]; [p.(Gly863Ala,Gly863del];(Asn1868Ile)] (1.5 PM3 points; PM3; PMID:37705246). Another missense variant, c.3322C>T;p.Arg1108Cys (ClinVarID: 92867), in the same codon has been classified as pathogenic for ABCA4-related retinopathy by the ClinGen ABCA4 VCEP, and Splice AI revealed no expected effects on splicing meeting PM5. 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 1.0.0: PM2_Supporting, PP3_Moderate, PM5, PS4, PM3.

Met criteria codes

PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 87.3 and the CI is 26.27- 456.18, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1 (PS4; PMID: 35120629).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.843 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate). No splice impact predicted by SpliceAI.
PM3	✔	This variant has been detected in multiple individuals with ABCA4-related retinopathy. Of those individuals, three were compound heterozygous for the variant and a pathogenic or likely pathogenic variant but none were owere confirmed in trans (c.6416G>C;p.Arg2139Pro, [c.2588G>C;5603A>T]; [p.(Gly863Ala,Gly863del];(Asn1868Ile)] (1.5 PM3 points; PM3; PMID:37705246).
PM5	✔	Another missense variant, c.3322C>T;p.Arg1108Cys (ClinVarID: 92867), in the same codon has been classified as pathogenic for ABCA4-related retinopathy by the ClinGen ABCA4 VCEP, and Splice AI revealed no expected effects on splicing (PM5).
PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.0000465 (75/1614058 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001).

Curation History

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