Variant: NM_000350.3(ABCA4):c.2588G>C (p.Gly863Ala)

Version: 2.0

CA119128

7879 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: c19472a2-3c5b-40bc-aced-cb58564a4b6d
Approved on: 2026-01-27
Published on: 2026-01-29

HGVS expressions

NM_000350.3:c.2588G>C
NM_000350.3(ABCA4):c.2588G>C (p.Gly863Ala)
NC_000001.11:g.94051698C>G
CM000663.2:g.94051698C>G
NC_000001.10:g.94517254C>G
CM000663.1:g.94517254C>G
NC_000001.9:g.94289842C>G
NG_009073.1:g.74452G>C
ENST00000370225.4:c.2588G>C
ENST00000649773.1:c.2366G>C
ENST00000370225.3:c.2588G>C
ENST00000536513.5:c.-65+11476G>C
NM_000350.2:c.2588G>C

Uncertain Significance

Met criteria codes 2

PP3_Moderate PS3_Supporting

Not Met criteria codes 3

PM3 BS1 PS4

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.2588G>C variant in ABCA4 is a missense variant predicted to cause substitution of glycine by alanine at amino acid 863; p.Gly863Ala. The computational predictor REVEL gives a score of 0.798 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate). There are many individuals with ABCA4-retinopathies reported with this variant. However, many of these individuals may also have the ABCA4 c.5603A>T, p.Asn1868Ile variant in cis variant. Due to its frequency in controls, many studies previously considered the p.Asn1868Ile variant to be benign and not consistently reported in the literature.

Therefore, no cases were counted for the variant as the presence or absence of the p.Asn1868Ile variant could not be confirmed, and the complex allele is curated separately. The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls; however, we confirmed with the authors that some of the affected individuals had the complex allele, so the effect of the variant alone was not considered in this calculation (PS4 not applied; PMID: 35120629). ABCA4 ATPase activity in HEK293 cells showed an approximately 75% reduction of basal and retinal-stimulated ATPase, indicating that this variant impacts protein function (PS3_Supporting; PMID: 11017087). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for ABCA4-related retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen ABCA4 VCEP (Specification Version 1): PS3_Supporting, PP3_Moderate.

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.798 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PS3_Supporting	✔	ABCA4 ATPase activity in HEK293 cells showed an approximately 75% reduction of basal and retinal-stimulated ATPase, indicating that this variant impacts protein function (PS3_Supporting; PMID: 11017087).

Not Met criteria codes

PM3	✖	This variant has been detected in at least 3 individuals with ABCA4-related retinopathy that do not report the complex allele with the ABCA4 p.Asn1868Ile variant. However, given the p.Asn1868Ile variant was at one time thought to be benign, we fear this variant is possibly under reported. Therefore, we will not count any probands until we have evidence that the p.Asn1868Ile variant was not in cis with the p. Gly863Ala variant.
BS1	✖	The GroupMax filtering allele frequency in gnomAD v4.1.0 is 0.008753, which is greater than the ClinGen ABCA4 VCEP's threshold for BS1_Supporting (>0.00163); however, this variant is on the ABCA4 BS1 Exclusion List. https://gnomad.broadinstitute.org/variant-cooccurrence?dataset=gnomad_r2_1&variant=1-94476467-T-A&variant=1-94517254-C-G Calculated frequency using haplotypes: 0.0043605693
PS4	✖	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 5.8 and the CI is 5.14-6.64, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1. However, upon contacting the authors, we were informed that this calculation included individuals with the complex allele. Therefore, this value is not a true representation of the effect of this variant alone (PS4; PMID: 35120629).

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000350.3(ABCA4):c.2588G>C (p.Gl...	Uncertain Significance	ABCA4-Related Retinopathy	2026-01-29	2.0	ClinGen ABCA4 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCA4 Version 1.0.0	ABCA4
View	NM_000350.3(ABCA4):c.2588G>C (p.Gl...	Pathogenic	ABCA4-Related Retinopathy	2025-12-19	1.0	ClinGen ABCA4 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCA4 Version 1.0.0	ABCA4

Showing 1 to 2 of 2 rows