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Variant: NM_000350.3(ABCA4):c.2894A>G (p.Asn965Ser)

Version: 1.0

CA958124

236096 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: d3a67c98-4364-4764-bfd8-bb0bb1793b17
Approved on: 2026/6/23
Published on: 2026/7/28

HGVS expressions

NM_000350.3(ABCA4):c.2894A>G (p.Asn965Ser)
NM_000350.3:c.2894A>G
NC_000001.11:g.94046943T>C
CM000663.2:g.94046943T>C
NC_000001.10:g.94512499T>C
CM000663.1:g.94512499T>C
NC_000001.9:g.94285087T>C
NG_009073.1:g.79207A>G
ENST00000370225.4:c.2894A>G
ENST00000649773.1:c.2672A>G
ENST00000370225.3:c.2894A>G
ENST00000536513.5:c.-64-6854A>G
NM_000350.2:c.2894A>G

Pathogenic

Met criteria codes 4

PP3_Moderate PS3 PS4 PM2_Supporting

Evidence Links 1

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*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

ABCA4 VCEP

The NM_000350.3:c.2894A>G variant in ABCA4 is a missense variant predicted to cause substitution of asparagine by serine at amino acid 965 (p.Asn965Ser). The total minor allele frequency in gnomAD v4.1.0 is 0.00007496 (121/1614088 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001). The computational predictor REVEL gives a score of 0.779 which is above the threshold of >0.772 (PP3_Moderate). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls with an OR of 75.4 and CI of 49.14 to 119.82, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not

contain 1 (PS4; PMID: 35120629). Experiments with transgenic p.Asn965Ser knock-in mice showed the variant expresses at half the level of wildtype ABCA4, partially mislocalized to the endoplasmic reticulum (ER) of photoreceptors, was devoid of N-Ret-PE activated ATPase activity, and caused an increase in autofluorescence and the bisretinoid A2E associated with lipofuscin deposits in retinal pigment epithelial cells, indicating loss of ABCA4 protein function (PS3; PMID: 29145636). 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, PS3, PP3, PM2_Supporting.

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.779 which is above the threshold of >0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Moderate).
PS3	✔	Experiments with transgenic p.Asn965Ser knock-in mice showed the variant expresses at half the level of wildtype ABCA4, partially mislocalized to the endoplasmic reticulum (ER) of photoreceptors, was devoid of N-Ret-PE activated ATPase activity, and caused an increase in autofluorescence and the bisretinoid A2E associated with lipofuscin deposits in retinal pigment epithelial cells, indicating loss of ABCA4 protein function (PS3; PMID: 29145636). p.Asn965Ser knockin mouse studies show that the variant expresses at half the level of WT ABCA4, partially mislocalizes to the endoplasmic reticulum (ER) of photoreceptors, is devoid of N-Ret-PE activated ATPase activity, and causes an increase in autofluorescence and the bisretinoid A2E associated with lipofuscin deposits in retinal pigment epithelial cells. PubMed:29145636
PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 75.4 and the CI is 49.14 to 119.82, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1 (PS4; PMID: 35120629).
PM2_Supporting	✔	The total minor allele frequency in gnomAD v4.1.0 is 0.00007496 (121/1614088 alleles), which is lower than the ClinGen ABCA4 VCEP's threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).

Curation History

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