Variant: NM_000350.3(ABCA4):c.5882G>A (p.Gly1961Glu)

Version: 1.0

CA119132

7888 (ClinVar)

Gene: ABCA4 (HGNC:24)
Condition: ABCA4-related retinopathy (MONDO:0800406)
Inheritance Mode: Autosomal recessive inheritance
UUID: b155123d-fb65-4b16-bae6-aaee58a92532
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HGVS expressions

NM_000350.3:c.5882G>A
NM_000350.3(ABCA4):c.5882G>A (p.Gly1961Glu)
NC_000001.11:g.94008251C>T
CM000663.2:g.94008251C>T
NC_000001.10:g.94473807C>T
CM000663.1:g.94473807C>T
NC_000001.9:g.94246395C>T
NG_009073.1:g.117899G>A
ENST00000370225.4:c.5882G>A
ENST00000370225.3:c.5882G>A
ENST00000465352.1:n.298G>A
ENST00000536513.5:c.2258G>A
NM_000350.2:c.5882G>A

Pathogenic

Met criteria codes 6

PM3_Very Strong | PP1_Strong | PS3_Supporting | PS4 | PP3 | PP4

Not Met criteria codes 3

BS1 | PS2 | PM2

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:c.5882G>A variant in ABCA4 is a missense variant predicted to cause substitution of glycine by glutamine at amino acid 1961 (p.Gly1961Glu). The computational predictor REVEL gives a score of 0.76, which is in the range of 0.644-0.772, evidence that predicts a damaging effect on ABCA4 function (PP3). This variant has been detected in hundreds of individuals with Stargardt disease (PMIDs: 29925512, 33909047). At least seven individuals were homozygous for the variant and at least three were compound heterozygous for the variant and another pathogenic variant in ABCA4, as confirmed in trans by parental testing (PMIDs: 25922843, 33909047; PM3_Very

Strong). At least one patient with this variant displayed presence of at least two ABCA4 variants, onset under 18 years of age, macular flecks on imaging, macular atrophy, central scotoma, choriocapillaris atrophy, and severely reduced visual acuity, which is highly specific for ABCA4-related retinopathy (PMID: 22661473; PP4). The variant has been reported to segregate with ABCA4-related retinopathy in affected individuals across at least six families. (PMIDs: 16896346, 19217903, 23769331, 31318848; PP1_Strong). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The odds ratio is 27.8 and the confidence interval is 24.81 to 31.13, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1 (PMID: 35120629; PS4). Measurement of ATPase activity in ABCA4 mutant transfected HEK293 cells showed G1961E exhibiting a reduced basal ATPase activity when inhibited by retinal, an indication of this variant's impact on protein function (PMID: 11017087; PS3_Supporting). Of note, this variant appears to be associated with a milder phenotype and may have no phenotype if inherited in a homozygous state with no other pathogenic ABCA4 variants (PMID: 38602673). 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 (v.1.0.0): PM3_Very Strong, PP1_Strong, PS4, PP3, PP4, PS3_Supporting.

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in over 150 individuals with Stargardt's disease (PMID: 33909047). Of those individuals, seven individuals were homozygous for the variant (PMID: 33099047) and at least three were compound heterozygous for the variant and another pathogenic variant confirmed in trans by parental testing (p.Arg152Ter, p.Trp15Ter, PMID: 33909047; p.Tyr872Ter, PMID: 25922843). Seven homozygous probands and three compound heterozygous proband totaled four points, qualifying for Very Strong strength level for PM3 as per specifications of the ClinGen ABCA4 VCEP. (PM3_Very Strong, 8 points).
PP1_Strong	✔	The variant has been reported to segregate with ABCA4-related retinopathy in affected individuals across at least six families. (PMID: 16896346, 19217903, 23769331, 31318848; PP1_Strong).
PS3_Supporting	✔	Measurement of ATPase activity in ABCA4 mutant transfected HEK293 cells showed G1961E exhibits a reduced basal ATPase activity that is inhibited by retinal, indicating that this variant impacts protein function (PMID: 11017087). (PS3_Supporting, 1 point)
PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls. The OR is 27.8 and the CI is 24.81 to 31.13, which is above the ABCA4 VCEP threshold of ≥5, where the CI does not contain 1 (PMID: 35120629, PS4, 4 points).
PP3	✔	The computational predictor REVEL gives a score of 0.76 which is in the range of 0.644-0.772, evidence that predicts a damaging effect on ABCA4 function (PP3_Supporting, 1 point).
PP4	✔	At least one patient with this variant displayed presence of at least two ABCA4 variants, onset under 18 years of age, macular flecks on imaging and fundus autofluorescence, severely reduced visual acuity, severe central macular atrophy, and central scotomata, which is highly specific for ABCA4-related retinopathy (PP4_Supporting, PMID: 22661473). (PP4_Supporting, 1 point)

Not Met criteria codes

BS1	✖	The GroupMax filtering allele frequency in gnomAD v4.1.0 is 0.01768, which is greater than the ClinGen ABCA4 VCEP's threshold for BS1 (>0.0163); however this variant is excluded from applying the BA1/BS1 codes.
PS2	✖	

This variant has been identified as a de novo occurrence with unconfirmed parental relationships in one individual with ABCA4-related retinopathy and the proband proband has a known pathogenic variant with the de novo variant . No del/dup testing for mother. Phenotype doesn't fit. (PS2_Moderate not met; PMID: 38694055)

PM2	✖	The total minor allele frequency in gnomAD v4.1.0 is 0.003406 (5498/1614012 alleles) which is higher than the ClinGen ABCA4 VCEP threshold of 0.0001 for PM2. (PM2 is not met)

Curation History

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