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Variant: NM_014336.5(AIPL1):c.50T>C (p.Leu17Pro)

Version: 1.0

CA8328674

870937 (ClinVar)

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3e77b2c1-9e59-4e01-acfe-ccfccfcb86a2
Approved on: 2025/9/29
Published on: 2025/9/29

HGVS expressions

NM_014336.5:c.50T>C
NM_014336.5(AIPL1):c.50T>C (p.Leu17Pro)
NC_000017.11:g.6435055A>G
CM000679.2:g.6435055A>G
NC_000017.10:g.6338375A>G
CM000679.1:g.6338375A>G
NC_000017.9:g.6279099A>G
NG_008474.1:g.5145T>C
ENST00000381129.8:c.50T>C
ENST00000250087.9:c.50T>C
ENST00000381128.2:c.50T>C
ENST00000381129.7:c.50T>C
ENST00000570466.5:c.50T>C
ENST00000570584.5:c.25T>C
ENST00000571740.5:c.50T>C
ENST00000574506.5:c.50T>C
ENST00000574913.1:c.50T>C
ENST00000575265.5:c.50T>C
ENST00000576307.5:c.50T>C
ENST00000576776.5:c.50T>C
ENST00000621374.4:c.50T>C
NM_001033054.2:c.50T>C
NM_001033055.2:c.50T>C
NM_001285399.2:c.50T>C
NM_001285400.2:c.50T>C
NM_001285401.2:c.50T>C
NM_001285402.1:c.-126T>C
NM_001285403.2:c.50T>C
NM_014336.4:c.50T>C
NM_001033054.3:c.50T>C
NM_001033055.3:c.50T>C
NM_001285399.3:c.50T>C
NM_001285400.3:c.50T>C
NM_001285401.3:c.50T>C
NM_001285402.2:c.-126T>C
NM_001285403.3:c.50T>C
NM_001285403.4:c.50T>C

Likely Pathogenic

Met criteria codes 6

PM2_Supporting | PP1 | PM3 | PS3_Supporting | PP4_Moderate | PP3_Moderate

Evidence Links 1

Expert Panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for AIPL1 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

NM_014336.5(AIPL1):c.50T>C (p.Leu17Pro) is a missense variant predicted to replace leucine with proline at amino acid 17. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 6.195e-7, with 1 / 1614234 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Lys214Asn variant (currently unclassified) confirmed in trans (0.25 points, PMID:21900377). This variant has also been reported in 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, PMID: 24265693). A second homozygous patient was reported (PMID:32531858) but was not counted towards PM3 because the phenotype was listed as arRP with no age of onset. A third homozygous patient with LCA was reported by a VCEP member (0.5 pts) (1.25 total points, PM3). At least one proband harboring this variant exhibits a phenotype including severely reduced electroretinogram responses from both rods (0.5 pts) and cones (1 pt) and was diagnosed with LCA (0.5 pts) within the first year of life (1 pt). Additional phenotypes include nystagmus (1 pt), sluggish pupils (0.5 pts), photophobia (1 pt), vascular attenuation, RPE mottling (0.5 pts) severe visual field loss (1 pt), and central macular atrophy. LCA gene panel screening revealed no other likely variants (2 pts). Together these are highly specific for AIPL1-related retinopathy (total 9 points, PMID: 21900377, PP4_Moderate). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 21900377). The computational predictor REVEL gives a score of 0.83, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on AIPL1 protein function (PP3_Moderate). Cells exogenously expressing the variant protein exhibit more than 60% reduction of cGMP levels relative to the wild-type control, which was equivalent to the control lacking AIPL1, while the variant protein exhibits loss of interaction with HSP90α and HSP90β in yeast-2-hybrid and ELISA experiments (PMID: 28973376). In summary, this variant meets the criteria to be classified as Likely Pathogenic for AIPL1-related retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PP4_moderate, PP1, PM2_supporting, PM3, PP3_moderate, and PS3_Supporting. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 6.195e-7, with 1 / 1614234 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 21900377).
PM3	✔	

This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Lys214Asn variant (currently unclassified) confirmed in trans (0.25 points, PMID:21900377). This variant has also been reported in 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, PMID: 24265693). A second homozygous patient was reported (PMID:32531858) but was not counted towards PM3 because the phenotype was listed as arRP with no age of onset. A third homozygous patient with LCA was reported by a VCEP member (0.5 pts) (1.25 total points, PM3).

PS3_Supporting ✔

Cells exogenously expressing the variant protein exhibit more than 60% reduction of cGMP levels relative to the wild-type control, which was equivalent to the control lacking AIPL1, while the variant protein exhibits loss of interaction with HSP90α and HSP90β in yeast-2-hybrid and ELISA experiments (PMID: 28973376).

Cells exogenously expressing the variant protein exhibit more than 60% reduction of cGMP levels relative to the wild-type control, which was equivalent to the control lacking AIPL1 (PMID: 28973376, Figure 8A).
PubMed:28973376

PP4_Moderate ✔

At least one proband harboring this variant exhibits a phenotype including severely reduced rod and cone ERG responses (1.5 pts) and was diagnosed with LCA (0.5 pts) within the first year of life (1 pt). Additional phenotypes include nystagmus (1 pt), sluggish pupils (0.5 pts), photophobia (1 pt), vascular attenuation, RPE mottling (0.5 pts) severe visual field loss (1 pt), and central macular atrophy. LCA gene panel screening revealed no other likely variants (2 pts). Together these are highly specific for AIPL1-related recessive retinopathy (total 9 points, PMID: 21900377, PP4_Moderate).

PP3_Moderate ✔

The computational predictor REVEL gives a score of 0.83, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on AIPL1 protein function (PP3_Moderate).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_014336.5(AIPL1):c.50T>C (p.Leu17...	Likely Pathogenic	AIPL1-Related Retinopathy	2025-09-29	1.0	ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for AIPL1 Version 1.0.0	AIPL1

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