Variant: NM_014336.5(AIPL1):c.1126C>T (p.Pro376Ser)

Version: 1.0

CA203312

65708 (ClinVar)

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5a69bac5-904d-4762-be15-7e88071e00b1
Approved on: 2025-09-29
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HGVS expressions

NM_014336.5:c.1126C>T
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NC_000017.11:g.6425489G>A
CM000679.2:g.6425489G>A
NC_000017.10:g.6328809G>A
CM000679.1:g.6328809G>A
NC_000017.9:g.6269533G>A
NG_008474.1:g.14711C>T
ENST00000381129.8:c.1126C>T
ENST00000250087.9:c.937C>T
ENST00000381128.2:c.*998C>T
ENST00000381129.7:c.1126C>T
ENST00000570466.5:c.1060C>T
ENST00000570584.5:c.251+8430C>T
ENST00000574506.5:c.1090C>T
ENST00000575265.5:c.*1097C>T
ENST00000576307.5:c.946C>T
ENST00000576776.5:c.1054C>T
ENST00000621374.4:c.*144C>T
NM_001033054.2:c.937C>T
NM_001033055.2:c.946C>T
NM_001285399.2:c.1090C>T
NM_001285400.2:c.1060C>T
NM_001285401.2:c.1054C>T
NM_001285402.1:c.1009C>T
NM_014336.4:c.1126C>T
NM_001033054.3:c.937C>T
NM_001033055.3:c.946C>T
NM_001285399.3:c.1090C>T
NM_001285400.3:c.1060C>T
NM_001285401.3:c.1054C>T
NM_001285402.2:c.1009C>T
NM_001285403.3:c.*1097C>T
NM_001285403.4:c.*1097C>T

Benign

Met criteria codes 3

BS2 **BP4** **BA1**

Not Met criteria codes 1

BS3

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.1126C>T (p.Pro376Ser) is a missense variant in exon 6 of 6 that is predicted to replace proline with serine at amino acid p.376. This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.06125, with 4,695 alleles / 74,822 total alleles and 166 homozygotes in the African/African American population, which is higher than the ClinGen LCA/eoRD VCEP BA1 threshold of >0.0057 (BA1). The variant has been found in the homozygous state in 170 adult individuals in gnomAD which exceeds the LCA/eoRD VCEP threshold of ≥6 (gnomAD version 4.1.0; BS2). The computational predictor REVEL gives a score of 0.129, which is below the ClinGen LCA/eoRD VCEP threshold of ≤0.183 and predicts a non-damaging effect on AIPL1 protein function. In addition, the splicing impact predictor SpliceAI gives a delta score of 0.00, which is below the ClinGen LCA/eoRD VCEP recommended threshold of <0.1 and does not predict an impact on splicing (BP4_Moderate). In summary, this variant meets the criteria to be classified as Benign for AIPL1-related retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: BA1, BS2, and BP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

BS2	ℹ	✓	The variant has been found in the homozygous state in 170 adult individuals in gnomAD which exceeds the LCA/eoRD VCEP threshold of ≥6 (gnomAD version 4.1.0; BS2).
BP4	ℹ	✓	The computational predictor REVEL gives a score of 0.129, which is below the ClinGen LCA/eoRD VCEP threshold of ≤0.183 and predicts a non-damaging effect on AIPL1 protein function. In addition, the splicing impact predictor SpliceAI gives a delta score of 0.00, which is below the ClinGen LCA/eoRD VCEP recommended threshold of <0.1 and does not predict an impact on splicing (BP4_Moderate).
BA1	ℹ	✓	This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 0.06125, with 4,695 alleles / 74,822 total alleles and 166 homozygotes in the African/African American population, which is higher than the ClinGen LCA/eoRD VCEP BA1 threshold of >0.0057 (BA1).

Not Met criteria codes

BS3		✗	The variant exhibits similar expression relative to the wild-type AIPL1 control, and co-expression of the variant with PDE6C and Pγ resulted in cGMP hydrolysis activity equivalent to the wild-type (PMID: 33067476). The variant did not exhibit aggregation or abnormal subcellular distribution in COS-7 cells (PMID: 33067476). However, these assays are not approved to meet BS3_Supporting.

The variant exhibits similar interaction with HSP90α and HSP90β relative to the wild-type AIPL1 control (Figure 6a) and co-expression of the variant with PDE6C and Pγ resulted in cGMP hydrolysis activity equivalent to the wild-type (Figure 6b). However, these assays are not approved to meet BS3_Supporting. The variant did not exhibit aggregation or abnormal subcellular distribution in CHO and HEK293T cells (Figure 4). PubMed:33067476

Curation History

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