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Variant: NM_001285403.4:c.126T>A

Version: 1.0

CA397397658

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: df7ed658-ed3d-4088-99d8-99fb3f290094
Approved on: 2025/9/29
Published on: 2025/9/29

HGVS expressions

NM_001285403.4:c.126T>A
NC_000017.11:g.6434069A>T
CM000679.2:g.6434069A>T
NC_000017.10:g.6337389A>T
CM000679.1:g.6337389A>T
NC_000017.9:g.6278113A>T
NG_008474.1:g.6131T>A
ENST00000381129.8:c.126T>A
ENST00000250087.9:c.126T>A
ENST00000381128.2:c.184T>A
ENST00000381129.7:c.126T>A
ENST00000570466.5:c.97-37T>A
ENST00000570584.5:c.101T>A
ENST00000571740.5:c.126T>A
ENST00000574506.5:c.97-7T>A
ENST00000574913.1:c.126T>A
ENST00000575265.5:c.126T>A
ENST00000576307.5:c.96+940T>A
ENST00000576776.5:c.126T>A
ENST00000621374.4:c.126T>A
NM_001033054.2:c.126T>A
NM_001033055.2:c.96+940T>A
NM_001285399.2:c.97-7T>A
NM_001285400.2:c.97-37T>A
NM_001285401.2:c.126T>A
NM_001285402.1:c.9T>A
NM_001285403.2:c.126T>A
NM_014336.4:c.126T>A
NM_001033054.3:c.126T>A
NM_001033055.3:c.96+940T>A
NM_001285399.3:c.97-7T>A
NM_001285400.3:c.97-37T>A
NM_001285401.3:c.126T>A
NM_001285402.2:c.9T>A
NM_001285403.3:c.126T>A
NM_014336.5:c.126T>A

Pathogenic

Met criteria codes 4

PM3_Supporting PP4 PM2_Supporting PVS1

Evidence Links 0

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.126T>A (p.Cys42Ter) is a nonsense variant that introduces a premature stop codon into exon 2 of 6 and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_014336.5(AIPL1):c.784G>A (p.Gly262Ser) variant suspected but not confirmed in trans (0.5 points, PMID: 15249368), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (PM3_Supporting). At least one proband harboring this variant exhibits a phenotype including a diagnosis of Leber congenital amaurosis (0.5 pts) with visual acuity limited to hand movements (1 pt), mild maculopathy (0.5 pts), mild optic nerve pallor (0.5 pts), severe pigmentary retinopathy (1 pt), and photoattraction (1 pt), which together are specific for AIPL1-related retinopathy (total 4.5 points, PMID: 15249368, PP4). In summary, this variant meets the criteria to be classified as Pathogenic for AIPL1-related retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PVS1, PM2_Supporting, PM3_Supporting, and PP4. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PM3_Supporting	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_014336.5(AIPL1):c.784G>A (p.Gly262Ser) variant suspected but not confirmed in trans (0.5 points, PMID: 15249368), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (PM3_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including a diagnosis of Leber congenital amaurosis (0.5 pts) with visual acuity limited to hand movements (1 pt), mild maculopathy (0.5 pts), mild optic nerve pallor (0.5 pts), severe pigmentary retinopathy (0.5 pts), and photoattraction (1 pt), which together are specific for AIPL1-related recessive retinopathy (total 4 points, PMID: 15249368, PP4).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1	✔	This is a nonsense variant that introduces a premature stop codon into exon 2 of 6 and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1).

Curation History

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