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Variant: NM_001285403.4:c.214T>C

Version: 1.0

CA397397299

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: aa5e7a2b-282b-4e07-b134-48139d01bf31
Approved on: 2025/9/29
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HGVS expressions

NM_001285403.4:c.214T>C
NC_000017.11:g.6433981A>G
CM000679.2:g.6433981A>G
NC_000017.10:g.6337301A>G
CM000679.1:g.6337301A>G
NC_000017.9:g.6278025A>G
NG_008474.1:g.6219T>C
ENST00000381129.8:c.214T>C
ENST00000250087.9:c.214T>C
ENST00000381128.2:c.*86T>C
ENST00000381129.7:c.214T>C
ENST00000570466.5:c.148T>C
ENST00000570584.5:c.189T>C
ENST00000571740.5:c.214T>C
ENST00000574506.5:c.178T>C
ENST00000574913.1:c.214T>C
ENST00000575265.5:c.214T>C
ENST00000576307.5:c.96+1028T>C
ENST00000576776.5:c.214T>C
ENST00000621374.4:c.214T>C
NM_001033054.2:c.214T>C
NM_001033055.2:c.96+1028T>C
NM_001285399.2:c.178T>C
NM_001285400.2:c.148T>C
NM_001285401.2:c.214T>C
NM_001285402.1:c.97T>C
NM_001285403.2:c.214T>C
NM_014336.4:c.214T>C
NM_001033054.3:c.214T>C
NM_001033055.3:c.96+1028T>C
NM_001285399.3:c.178T>C
NM_001285400.3:c.148T>C
NM_001285401.3:c.214T>C
NM_001285402.2:c.97T>C
NM_001285403.3:c.214T>C
NM_014336.5:c.214T>C

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS3_Supporting PP4_Moderate PP3_Moderate

Not Met criteria codes 1

PM3

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.214T>C (p.Trp72Arg) is a missense variant predicted to replace tryptophan with arginine at amino acid p.72. 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 M_014336.5(AIPL1):c.265T>C (p.Cys89Arg) variant suspected in trans (PMID: 20702822, PMID: 23847139, PMID: 33067476), which was previously classified likely pathogenic by the ClinGen LCA/eoRD VCEP (0.25 points), so the PM3_Supporting code was not met. At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with genotyping by a next-generation sequencing panel of 163 known inherited retinal disease-associated genes (2 pts), severe visual disturbances in infancy or early childhood (1 pt), visual acuity limited to light perception (1 pt), moderate hypermetropia, kinetic visual field extent not detectable (1 pt), keratoconus (0.5 pts), nystagmus (1 pt), posterior subcapsular cataract (0.5 pts), and nondetectable electroretinogram responses from both rods (0.5 pts) and cones (1 pt), which together are highly specific for AIPL1-related retinopathy (total 9 points, PMID: 20702822, PMID: 23847139, PP4_Moderate). The variant was associated with ~40% PDE6 enzymatic activity in a cGMP hydrolysis assay relative to the wild-type control, which was comparable to the negative control lacking AIPL1, indicating that it triggers a severe defect in protein function (PMID: 33067476, PS3_Supporting). The computational predictor REVEL gives a score of 0.836, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on AIPL1 protein function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.01 for acceptor gain, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. 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: PM2_Supporting, PP4_Moderate, PS3_Supporting, and PP3_Moderate. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS3_Supporting	✔	The variant was associated with ~40% PDE6 enzymatic activity in a cGMP hydrolysis assay relative to the wild-type control, which was comparable to the negative control lacking AIPL1, indicating that it triggers a severe defect in protein function (PMID: 33067476, PS3_Supporting).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with genotyping by a next-generation sequencing panel of 163 known inherited retinal disease-associated genes (2 pts), severe visual disturbances in infancy or early childhood (1 pt), visual acuity limited to light perception (1 pt), moderate hypermetropia, kinetic visual field extent not detectable (1 pt), keratoconus (0.5 pts), nystagmus (1 pt), posterior subcapsular cataract (0.5 pts), and nondetectable electroretinogram responses from both rods (0.5

pts) and cones (1 pt), which together are highly specific for AIPL1-related retinopathy (total 9 points, PMID: 20702822, PMID: 23847139, PP4_Moderate).

PP3_Moderate ✔

The computational predictor REVEL gives a score of 0.836, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on AIPL1 protein function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.01 for acceptor gain, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.

Not Met criteria codes

PM3 ✖

This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the M_014336.5(AIPL1):c.265T>C (p.Cys89Arg) variant suspected in trans (PMID: 20702822, PMID: 23847139, PMID: 33067476), which was previously classified likely pathogenic by the ClinGen LCA/eoRD VCEP (0.25 points), so the PM3_Supporting code was not met.

Curation History

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