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Variant: NM_014336.5(AIPL1):c.715T>C (p.Cys239Arg)

Version: 1.0

CA227892

5567 (ClinVar)

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: a14e8f72-a3a8-4337-bcd0-87d192da8977
Approved on: 2025/9/29
Published on: 2025/9/29

HGVS expressions

NM_014336.5:c.715T>C
NM_014336.5(AIPL1):c.715T>C (p.Cys239Arg)
NC_000017.11:g.6426684A>G
CM000679.2:g.6426684A>G
NC_000017.10:g.6330004A>G
CM000679.1:g.6330004A>G
NC_000017.9:g.6270728A>G
NG_008474.1:g.13516T>C
ENST00000381129.8:c.715T>C
ENST00000250087.9:c.526T>C
ENST00000381128.2:c.*587T>C
ENST00000381129.7:c.715T>C
ENST00000570466.5:c.649T>C
ENST00000570584.5:c.251+7235T>C
ENST00000571740.5:c.691T>C
ENST00000574506.5:c.679T>C
ENST00000575265.5:c.715T>C
ENST00000576307.5:c.535T>C
ENST00000576776.5:c.643T>C
ENST00000621374.4:c.715T>C
NM_001033054.2:c.526T>C
NM_001033055.2:c.535T>C
NM_001285399.2:c.679T>C
NM_001285400.2:c.649T>C
NM_001285401.2:c.643T>C
NM_001285402.1:c.598T>C
NM_001285403.2:c.691T>C
NM_014336.4:c.715T>C
NM_001033054.3:c.526T>C
NM_001033055.3:c.535T>C
NM_001285399.3:c.679T>C
NM_001285400.3:c.649T>C
NM_001285401.3:c.643T>C
NM_001285402.2:c.598T>C
NM_001285403.3:c.691T>C
NM_001285403.4:c.691T>C

Likely Pathogenic

Met criteria codes 6

PP1_Moderate PP3_Moderate PP4_Moderate PM3_Supporting PM2_Supporting PS3_Supporting

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.715T>C (p.Cys239Arg) is predicted to replace the cysteine at position p.239 with arginine. 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 homozygous for the variant (PMID: 15249368) (0.5 total points, PM3_Supporting). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PP1_Moderate; PMID: 15249368 and personal communication). At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) with poor central vision (1 pt) from birth (1 pt), along with severe night blindness (0.5 pts) and pendular nystagmus (1 pt). Full-field electroretinogram responses were non-detectable from both rods (0.5 pts) and cones (1 pt). Visual acuity 20/800 in both eyes at age 17. Fundus examination revealed widespread RPE changes with pigment clumping (0.5 pt), attenuated retinal vessels (1 pt), macular atrophy (0.5 pts) and a pale optic disk (0.5 pts) which together are specific for AIPL1-related retinopathy (total 8 points, PMID: 10873396, PP4_Moderate). The variant protein exhibits less than 10% of wild-type AIPL1 activity in a cGMP hydrolysis assay based on exogenous expression in HEK293T cells (PMID: 27268253, PS3_Supporting). the computational predictor REVEL gives a score of 0.789, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on AIPL1 protein function (PP3_Moderate). 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, PP3_Moderate, PS3_Supporting, PM3_Supporting, PP1_Moderate, and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PP1_Moderate ✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PP1_Moderate; PMID: 15249368)
PP3_Moderate ✔	The computational predictor REVEL gives a score of 0.789, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on AIPL1 protein function (PP3_Moderate).
PP4_Moderate ✔	At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) with poor central vision (1 pt) from birth (1 pt), along with severe night blindness (0.5 pts) and pendular nystagmus (1 pt). Full-field ERGs were non-detectable (rod and cone) (1.5 pts). Visual acuity 20/800 in both eyes at age 17. Fundus examination revealed widespread RPE changes with pigment clumping (0.5 pt), attenuated retinal vessels (1 pt), macular atrophy (0.5 pts) and a pale optic disk (0.5 pts) which together are specific for AIPL1-related retinopathy (total 8 points, PMID: 10873396, PP4).
PM3_Supporting ✔	

This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (PMID: 15249368) (0.5 total points, PM3_Supporting).

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS3_Supporting	✔	The variant protein exhibits less than 10% of wild-type AIPL1 activity in a cGMP hydrolysis assay based on exogenous expression in HEK293T cells (PMID: 27268253, PS3_Supporting). The variant protein exhibits less than 10% of wild-type AIPL1 activity in a cGMP hydrolysis assay based on exogenous expression in HEK293T cells (PMID: 27268253, Figures 5B, 5C). PubMed:27268253

Curation History

Showing 1 to 1 of 1 rows

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