Variant: NM_014336.5(AIPL1):c.190G>A (p.Gly64Arg)

Version: 1.0

CA8328596

867104 (ClinVar)

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2a574a72-c820-427e-b46f-17c343b0c9ff
Approved on: 2025-09-29
Published on: 2025-09-29

HGVS expressions

NM_014336.5:c.190G>A
NM_014336.5(AIPL1):c.190G>A (p.Gly64Arg)
NC_000017.11:g.6434005C>T
CM000679.2:g.6434005C>T
NC_000017.10:g.6337325C>T
CM000679.1:g.6337325C>T
NC_000017.9:g.6278049C>T
NG_008474.1:g.6195G>A
ENST00000381129.8:c.190G>A
ENST00000250087.9:c.190G>A
ENST00000381128.2:c.*62G>A
ENST00000381129.7:c.190G>A
ENST00000570466.5:c.124G>A
ENST00000570584.5:c.165G>A
ENST00000571740.5:c.190G>A
ENST00000574506.5:c.154G>A
ENST00000574913.1:c.190G>A
ENST00000575265.5:c.190G>A
ENST00000576307.5:c.96+1004G>A
ENST00000576776.5:c.190G>A
ENST00000621374.4:c.190G>A
NM_001033054.2:c.190G>A
NM_001033055.2:c.96+1004G>A
NM_001285399.2:c.154G>A
NM_001285400.2:c.124G>A
NM_001285401.2:c.190G>A
NM_001285402.1:c.73G>A
NM_001285403.2:c.190G>A
NM_014336.4:c.190G>A
NM_001033054.3:c.190G>A
NM_001033055.3:c.96+1004G>A
NM_001285399.3:c.154G>A
NM_001285400.3:c.124G>A
NM_001285401.3:c.190G>A
NM_001285402.2:c.73G>A
NM_001285403.3:c.190G>A
NM_001285403.4:c.190G>A

Likely Pathogenic

Met criteria codes 5

PM3 PP3_Strong PS3_Supporting PM2_Supporting PP4

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.190G>A (p.Gly64Arg) is a missense variant predicted to replace glycine with arginine at amino acid p.64. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.00001921, with 31 / 1614006 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 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the p.Trp278Ter variant confirmed in trans (VCEP member data, 1 pt) and suspected in trans (PMID:22412862, PMID: 25596619, 0.5 points), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1.5 total points, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts), onset between birth and age ten years (1 pt), nystagmus (1 pt), RPE mottling (0.5 pts), and evidence of cone involvement on ERG (1 pt) which together are specific for AIPL1-related retinopathy (total 4 points, PMID: 22412862, PP4). The computational predictor REVEL gives a score of 0.949, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.93 and predicts a damaging effect on AIPL1 protein function (PP3_Strong). 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, PS3_Supporting). 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: PP3_Strong, PM3, PM2_Supporting, PP4, and PS3_Supporting. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PM3	✔	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the p.Trp278Ter variant confirmed in trans (VCEP member data, 1 pt) and suspected in trans (PMID:22412862, PMID: 25596619, 0.5 points), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1.5 total points, PM3).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.949, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.93 and predicts a damaging effect on AIPL1 protein function (PP3_Strong).
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 (PMID: 28973376).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.00001921, with 31/1614006 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).

PP4		✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts), onset between birth and age ten years (1 pt), nystagmus (1 pt), RPE mottling (0.5 pts), and evidence of cone involvement on ERG (1 pt) which together are specific for AIPL1-related recessive retinopathy (total 4 points, PMID: 22412862, PP4)

Curation History

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