Variant: NM_014336.5(AIPL1):c.401A>T (p.Tyr134Phe)

Version: 1.0

CA202389

196465 (ClinVar)

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: adf46226-3417-4578-ad21-3a2053d9c0df
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HGVS expressions

NM_014336.5:c.401A>T
NM_014336.5(AIPL1):c.401A>T (p.Tyr134Phe)
NC_000017.11:g.6428382T>A
CM000679.2:g.6428382T>A
NC_000017.10:g.6331702T>A
CM000679.1:g.6331702T>A
NC_000017.9:g.6272426T>A
NG_008474.1:g.11818A>T
ENST00000381129.8:c.401A>T
ENST00000250087.9:c.277-1325A>T
ENST00000381128.2:c.*273A>T
ENST00000381129.7:c.401A>T
ENST00000570466.5:c.335A>T
ENST00000570584.5:c.251+5537A>T
ENST00000571740.5:c.401A>T
ENST00000574506.5:c.365A>T
ENST00000574913.1:c.401A>T
ENST00000575265.5:c.401A>T
ENST00000576307.5:c.221A>T
ENST00000576776.5:c.401A>T
ENST00000621374.4:c.401A>T
NM_001033054.2:c.277-1325A>T
NM_001033055.2:c.221A>T
NM_001285399.2:c.365A>T
NM_001285400.2:c.335A>T
NM_001285401.2:c.401A>T
NM_001285402.1:c.284A>T
NM_001285403.2:c.401A>T
NM_014336.4:c.401A>T
NM_001033054.3:c.277-1325A>T
NM_001033055.3:c.221A>T
NM_001285399.3:c.365A>T
NM_001285400.3:c.335A>T
NM_001285401.3:c.401A>T
NM_001285402.2:c.284A>T
NM_001285403.3:c.401A>T
NM_001285403.4:c.401A>T

Benign

Met criteria codes 3

PP3_Moderate BA1 BS2

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.401A>T (p.Tyr134Phe) is a missense variant in exon 3 of 6 that is predicted to replace tyrosine with phenylalanine at amino acid p.134. This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.006905, with 8,298 alleles / 1,180,030 total alleles in the European (non-Finnish) population, which is higher than the ClinGen LCA/eoRD VCEP BA1 threshold of >0.0057 (BA1). It has also been found in the homozygous state in 49 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 0.845, 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 delta score of 0, which is below the ClinGen LCA/eoRD VCEP recommended threshold of <0.1 and does not predict an impact on splicing. The variant exhibited >90% enzymatic activity in a cGMP hydrolysis assay relative to the wild-type control, as well as cytoplasmic and nuclear localization similar to the wild-type (PMID: 27268253), however, these assays are not approved to meet BS3_Supporting. 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 PP3_Moderate. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.845, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on AIPL1 protein function. However, the in silico data is conflicting with an AlphaMissense score of 0.1054 supporting a benign variant, while other models are indeterminate. In addition, the splicing impact predictor SpliceAI gives a delta score of 0, which is below the ClinGen LCA/eoRD VCEP recommended threshold of <0.1 and does not predict an impact on splicing. Because the variant meets the BA1 code and the BS2 code with 49 homozygotes, the PP3 code is not used.
BA1	✔	This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 0.006905, with 8298 alleles /1180030 total alleles in the European (non-Finnish) population, which is higher than the ClinGen LCA/eoRD VCEP BA1 threshold of >0.0057 (BA1).
BS2	✔	This variant has been found in the homozygous state in 49 adult individuals in gnomAD which exceeds the LCA/eoRD VCEP threshold of ≥6 (gnomAD version 4.1.0; BS2).

Not Met criteria codes

BS3	✖	The variant exhibited >90% enzymatic activity in a cGMP hydrolysis assay relative to the wild-type control, as well as cytoplasmic and nuclear localization similar to the wild-type (PMID: 27268253), however, these assays are not approved to meet BS3_Supporting. The variant protein exhibits cytoplasmic and nuclear localization similar to wild-type AIPL1 in an immunofluorescence microscopy (PMID: 27268253, Figure 6B). PubMed:27268253

Curation History

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