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Variant: NM_014336.5(AIPL1):c.211G>T (p.Val71Phe)

Version: 1.0

CA8328593

812219 (ClinVar)

Gene: AIPL1 (HGNC:23746)
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: 94439f89-b156-4b35-8610-3e93493f1cb1
Approved on: 2025/9/29
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HGVS expressions

NM_014336.5(AIPL1):c.211G>T (p.Val71Phe)
NM_014336.5:c.211G>T
NC_000017.11:g.6433984C>A
CM000679.2:g.6433984C>A
NC_000017.10:g.6337304C>A
CM000679.1:g.6337304C>A
NC_000017.9:g.6278028C>A
NG_008474.1:g.6216G>T
ENST00000381129.8:c.211G>T
ENST00000250087.9:c.211G>T
ENST00000381128.2:c.*83G>T
ENST00000381129.7:c.211G>T
ENST00000570466.5:c.145G>T
ENST00000570584.5:c.186G>T
ENST00000571740.5:c.211G>T
ENST00000574506.5:c.175G>T
ENST00000574913.1:c.211G>T
ENST00000575265.5:c.211G>T
ENST00000576307.5:c.96+1025G>T
ENST00000576776.5:c.211G>T
ENST00000621374.4:c.211G>T
NM_001033054.2:c.211G>T
NM_001033055.2:c.96+1025G>T
NM_001285399.2:c.175G>T
NM_001285400.2:c.145G>T
NM_001285401.2:c.211G>T
NM_001285402.1:c.94G>T
NM_001285403.2:c.211G>T
NM_014336.4:c.211G>T
NM_001033054.3:c.211G>T
NM_001033055.3:c.96+1025G>T
NM_001285399.3:c.175G>T
NM_001285400.3:c.145G>T
NM_001285401.3:c.211G>T
NM_001285402.2:c.94G>T
NM_001285403.3:c.211G>T
NM_001285403.4:c.211G>T

Likely Pathogenic

Met criteria codes 5

PM3_Strong | PS3_Supporting | PP3_Moderate | 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.211G>T (p.Val71Phe) is a missense variant resulting in replacement of valine by phenylalanine at amino acid p.71. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000001239, with 2 / 1,614,150 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 homozygous for the variant (1 point, PMID: 15024725, PMID: 20079931, PMID: 20702822, PMID: 26306921). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_014336.5(AIPL1):c.216G>A (p.Trp72Ter) variant likely confirmed in trans due to their physical proximity (1 point, PMID: 20702822), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). The variant has been reported in an additional proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_014336.5(AIPL1):c.730GAG[1] (p.Glu245del) variant suspected in trans, which has not yet been classified by the ClinGen LCA/eoRD VCEP. At least one proband harboring this variant exhibits a phenotype including a diagnosis of Leber congenital amaurosis (0.5 pts) received before age 5 years (1 pt), severely reduced central visual acuity (1 pt), kinetic visual field extent (V-4e) undetectable (1 pt), nystagmus (1 pt), and nondetectable electroretinogram responses from both rods (0.5 pts) and cones (1 pt), which together are specific for AIPL1-related retinopathy (total 6 points, PMID: 20702822, PP4). The computational predictor REVEL gives a score of 0.780, 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 0.02 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. Co-expression of the variant with PDE6C and Pγ resulted in less than 10% of cGMP hydrolysis activity relative to the wild-type AIPL1 control (PMID: 27268253), while X-ray crystal structures of the wild-type and variant AIPL1 identified an inability of the variant to bind prenyl groups, which are relevant to AIPL1 interaction with the isoprenylated C-terminus of PDE6 (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: PM2_Supporting, PM3_Strong, PP3_Moderate, PS3_supporting and PP4. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PM3_Strong	✔	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMID: 15024725, PMID: 20079931, PMID: 20702822, PMID: 26306921, VCEP member-provided data, PM3). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_014336.5(AIPL1):c.216G>A (p.Trp72Ter) variant likely confirmed in trans due to their physical proximity (1 point, PMID: 20702822), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). The variant has been reported in an

additional proband with early-onset severe retinal dystrophy (PMID: 38880373) who was compound heterozygous with the NM_014336.5(AIPL1):c.730GAG[1] (p.Glu245del) variant suspected in trans, which has not yet been classified by the ClinGen LCA/eoRD VCEP. The variant has been reported in an additional proband with a potentially compatible diagnosis (VCEP member-provided data) who was compound heterozygous with the NM_014336.5(AIPL1):c.1127del (p.Pro376Argfs*42) suspected in trans, which has not yet been classified by the ClinGen LCA/eoRD VCEP.

PS3_Supporting	✔	Co-expression of the variant with PDE6C and Pγ resulted in less than 10% of cGMP hydrolysis activity relative to the wild-type AIPL1 control (PMID: 27268253), while X-ray crystal structures of the wild-type and variant AIPL1 identified an inability of the variant to bind prenyl groups, which are relevant to AIPL1 interaction with the isoprenylated C-terminus of PDE6 (PMID: 28973376).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.780, 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 0.02 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.
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000001239, with 2 / 1,614,150 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 a diagnosis of Leber congenital amaurosis (0.5 pts) received before age 5 years (1 pt), severely reduced central visual acuity (1 pt), kinetic visual field extent (V-4e) undetectable (1 pt), nystagmus (1 pt), and nondetectable electroretinogram responses from both rods (0.5 pts) and cones (1 pt), which together are specific for AIPL1-related retinopathy (total 6 points, PMID: 20702822, PP4).

Curation History

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