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Variant: NM_014336.5(AIPL1):c.724AAG[1] (p.Lys243del)

Version: 1.0

CA8328415

1419404 (ClinVar)

Gene: AIPL1
Condition: AIPL1-related retinopathy (MONDO:0100438)
Inheritance Mode: Autosomal recessive inheritance
UUID: 26888b4c-1df8-4b35-91f3-b7b87f6c1a8e
Approved on: 2025/9/29
Published on: 2025/9/29

HGVS expressions

NM_014336.5:c.724AAG[1]
NM_014336.5(AIPL1):c.724AAG[1] (p.Lys243del)
NC_000017.11:g.6426674_6426676del
CM000679.2:g.6426674_6426676del
NC_000017.10:g.6329994_6329996del
CM000679.1:g.6329994_6329996del
NC_000017.9:g.6270718_6270720del
NG_008474.1:g.13528_13530del
ENST00000381129.8:c.727_729del
ENST00000250087.9:c.538_540del
ENST00000381128.2:c.*599_*601del
ENST00000381129.7:c.727_729del
ENST00000570466.5:c.661_663del
ENST00000570584.5:c.251+7247_251+7249del
ENST00000571740.5:c.703_705del
ENST00000574506.5:c.691_693del
ENST00000575265.5:c.727_729del
ENST00000576307.5:c.547_549del
ENST00000576776.5:c.655_657del
ENST00000621374.4:c.727_729del
NM_001033054.2:c.538_540del
NM_001033055.2:c.547_549del
NM_001285399.2:c.691_693del
NM_001285400.2:c.661_663del
NM_001285401.2:c.655_657del
NM_001285402.1:c.610_612del
NM_001285403.2:c.703_705del
NM_014336.4:c.727_729del
NM_001033054.3:c.538_540del
NM_001033055.3:c.547_549del
NM_001285399.3:c.691_693del
NM_001285400.3:c.661_663del
NM_001285401.3:c.655_657del
NM_001285402.2:c.610_612del
NM_001285403.3:c.703_705del
NM_014336.5:c.727_729del
NM_001285403.4:c.703_705del

Likely Pathogenic

Met criteria codes 4

PM4_Supporting | PP4 | PM3_Strong | PM2_Supporting

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.727_729del (p.Lys243del) is an in-frame deletion of three nucleotides predicted to cause a change in the length of the protein due to deletion of 1 amino acid in a non-repeat region, with at least one of the deleted base pairs highly conserved with a PhyloP conservation score of 2.5 (PM4_Supporting). This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.00001115, with 18 / 1,614,218 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 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, VCEP member-provided data). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_014336.5(AIPL1):c.834G>A (p.Trp278Ter) variant suspected in trans (0.5 points, PMID: 32865313), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP, or the NM_014336.5(AIPL1):c.190G>A (p.Gly64Arg) variant confirmed in trans (1 point, VCEP member-provided data, Blueprint Genetics), which was previously classified likely pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). A fourth proband with retinal dystrophy has been reported harboring the variant in the compound heterozygous state with the NM_014336.5(AIPL1):c.364G>A (p.Gly122Arg) variant, however, additional information will be required for inclusion in PM3 (VCEP member-provided data). At least one proband harboring this variant exhibits a phenotype including a diagnosis of Leber congenital amaurosis (0.5 pts) with light-seeking behavior (1 pt) from birth (1 pt), nystagmus (1 pt), central visual acuity limited to light perception (1 pt), and relatively normal fundus appearance at age 1 year with very mild granular RPE pigmentation (0.5 pts), which together are specific for AIPL1-related retinopathy (total 4 points, PMID: 32865313, PP4). 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: PM4_Supporting, PM2_Supporting, PM3_Strong, and PP4. (VCEP specifications version 1.0.0; date of approval 09/24/2025).

Met criteria codes

PM4_Supporting	✔	This variant is predicted to cause a change in the length of the protein due to an in-frame deletion encoding 1 amino acids in a non-repeat region, with at least one of the deleted base pairs highly conserved with a PhyloP conservation score of 2.5 (PM4_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including a diagnosis of Leber congenital amaurosis (0.5 pts) with light-seeking behavior (1 pt) from birth (1 pt), nystagmus (1 pt), central visual acuity limited to light perception (1 pt), and relatively normal fundus appearance at age 1 year with very mild granular RPE pigmentation (0.5 pts), which together are specific for AIPL1-related retinopathy (total 4 points, PMID: 32865313, PP4).

PM3_Strong		✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, VCEP member-provided data). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_014336.5(AIPL1):c.834G>A (p.Trp278Ter) variant suspected in trans (0.5 points, PMID: 32865313), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP, or the NM_014336.5(AIPL1):c.190G>A (p.Gly64Arg) variant confirmed in trans (1 point, VCEP member-provided data, Blueprint Genetics), which was previously classified likely pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). A fourth proband with retinal dystrophy has been reported harboring the variant in the compound heterozygous state with the NM_014336.5(AIPL1):c.364G>A (p.Gly122Arg) variant, however, additional information will be required for inclusion in PM3 (VCEP member-provided data).
PM2_Supporting		✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.00001115, with 18 / 1,614,218 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).

Curation History

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