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Variant: NM_000329.3(RPE65):c.1244C>T (p.Ala415Val)

Version: 1.1

CA16617183

421620 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: f548066b-0b8f-4134-a015-ff673e1f1743
Approved on: 2026/8/20
Published on: 2026/8/20

HGVS expressions

NM_000329.3:c.1244C>T
NM_000329.3(RPE65):c.1244C>T (p.Ala415Val)
NC_000001.11:g.68431376G>A
CM000663.2:g.68431376G>A
NC_000001.10:g.68897059G>A
CM000663.1:g.68897059G>A
NC_000001.9:g.68669647G>A
NG_008472.1:g.23584C>T
NG_008472.2:g.23584C>T
ENST00000262340.6:c.1244C>T
ENST00000262340.5:c.1244C>T
NM_000329.2:c.1244C>T

Likely Pathogenic

Met criteria codes 4

PM3_Supporting | PP4_Moderate | PM2_Supporting | PP3_Moderate

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 RPE65 Version 1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

NM_000329.3(RPE65):c.1244C>T is a missense variant causing substitution of alanine with valine at position p.415. This variant is present in gnomAD v.4.1.1 at a total allele frequency of 0.00000124, with 2 alleles / 1613336 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.886dup (p.Arg296fs) variant suspected in trans (PMID: 27102010, PMID: 30268864, PMID: 37660736), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (0.5

total points, PM3_Supporting). At least one proband harboring this variant has exhibited a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), onset before age 5 years (1 pt), flat ERG responses for rods (0.5 pts) and cones (1 pt), and improvement of night vision following RPE65 gene therapy (8 pts), which together are highly specific for RPE65-related recessive retinopathy (11 total pts, PMID: 37660736, PP4_Moderate). The computational predictor REVEL gives a score of 0.775, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). In summary, this variant meets the criteria to be classified as likely pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: PM2_Supporting, PM3_Supporting, PP3_Moderate, and PP4_Moderate. (LCA/eoRD VCEP specifications version 1.0).

Met criteria codes

PM3_Supporting ✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.886dup (p.Arg296fs) variant suspected in trans (PMID: 27102010, PMID: 30268864, PMID: 37660736), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (0.5 total points, PM3_Supporting). This variant is alternatively referred to as p.Lys294ins1gac.
PP4_Moderate ✔	At least one proband harboring this variant has exhibited a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), onset before age 5 years (1 pt), flat ERG responses for rods (0.5 pts) and cones (1 pt), and improvement of night vision following RPE65 gene therapy (8 pts), which together are highly specific for RPE65-related recessive retinopathy (11 total pts, PMID: 37660736, PP4_Moderate).
PM2_Supporting ✔	This variant is present in gnomAD v.4.1.1 at a total allele frequency of 0.00000124, with 2 alleles / 1613336 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PP3_Moderate ✔	The computational predictor REVEL gives the variant a score of 0.775, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Curation History

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