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Variant: NM_000329.3(RPE65):c.433G>C (p.Ala145Pro)

Version: 1.1

CA340747763

560497 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6efbe692-f348-4ee5-a148-6b8744bf4544
Approved on: 2026/8/20
Published on: 2026/8/20

HGVS expressions

NM_000329.3:c.433G>C
NM_000329.3(RPE65):c.433G>C (p.Ala145Pro)
NC_000001.11:g.68444593C>G
CM000663.2:g.68444593C>G
NC_000001.10:g.68910276C>G
CM000663.1:g.68910276C>G
NC_000001.9:g.68682864C>G
NG_008472.1:g.10367G>C
NG_008472.2:g.10367G>C
ENST00000262340.6:c.433G>C
ENST00000262340.5:c.433G>C
NM_000329.2:c.433G>C

Likely Pathogenic

Met criteria codes 6

PP4 PM3 PP3_Moderate PM2_Supporting PS3_Supporting PM5_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 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

The NM_000329.3(RPE65):c.433G>C (p.Ala145Pro) is a predicted missense variant that changes the alanine at position p.145 to proline. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.94, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The variant exhibited approximately 0% enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA/eoRD PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting,

unpublished data from VCEP member). At least one proband harboring this variant exhibits a phenotype including diagnosis of severe early onset retinal dystrophy or retinitis pigmentosa with onset during the first decade of life, genotyping by hereditary retinal dystrophy panel showing no alternative explanation for disease (2 pts), reduced visual acuity (1 pt), peripheral visual field constriction (1 pt), and macular atrophy (0.5 pts), which together are specific for RPE65-related recessive retinopathy (4.5 points, PMID: 36017377, PP4). This variant has been reported in at least 2 probands with hereditary retinal dystrophy with onset during the first decade of life who were homozygous for the variant (1 point, PMID: 36017377, 34315337). Two other missense variants at the same codon have been reported in similarly affected individuals (NM_000329.3(RPE65):c.434C>A (p.Ala145Asp) in PMIDs: 31273949 and 23661369, and NM_000329.3(RPE65):c.433G>A (p.Ala145Thr) in PMID: 26906952). The p.Ala145Asp variant has been classified as likely pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA/eoRD VCEP (PM5_Supporting). 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: PS3_Supporting, PM2_Supporting, PM3, PM5_Supporting, PP3_Moderate, and PP4. (LCA/eoRD VCEP specifications version 1.0.0).

Met criteria codes

PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of severe early onset retinal dystrophy or retinitis pigmentosa with onset during the first decade of life, genotyping by hereditary retinal dystrophy panel showing no alternative explanation for disease (2 pts), reduced visual acuity (1 pt), peripheral visual field constriction (1 pt), and macular atrophy (0.5 pts), which together are specific for RPE65-related recessive retinopathy (4.5 points, PMID: 36017377, PP4).
PM3	✔	This variant has been reported in at least 2 probands with hereditary retinal dystrophy with onset during the first decade of life who was homozygous for the variant (1/1 point, PMID: 36017377, 34315337). A second proband has been described harboring the variant in the homozygous state, but does not have sufficient phenotypic detail for inclusion in PM3 counting (PMID: 28224992). (1/1.5 total points, PM3).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.94, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (PM2_Supporting).
PS3_Supporting	✔	The variant exhibited approximately 0% enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, unpublished data from VCEP member).
PM5_Supporting	✔	Two other missense variants at the same codon have been reported in similarly affected individuals (NM_000329.3(RPE65):c.434C>A (p.Ala145Asp) in PMIDs: 31273949 and 23661369, and NM_000329.3(RPE65):c.433G>A (p.Ala145Thr) in PMID: 26906952). The p.Ala145Asp variant has been classified as likely pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PM5_Supporting). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants.

Curation History

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