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Variant: NM_000329.3(RPE65):c.430T>G (p.Tyr144Asp)

Version: 1.1

CA226550

98868 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5e6acb29-c2f8-443c-a4e2-a70d61308b32
Approved on: Tue, 22 Sep 2026 00:00:00 +0000
Published on: Tue, 22 Sep 2026 00:00:00 +0000

HGVS expressions

NM_000329.3(RPE65):c.430T>G (p.Tyr144Asp)
NM_000329.3:c.430T>G
NC_000001.11:g.68444596A>C
CM000663.2:g.68444596A>C
NC_000001.10:g.68910279A>C
CM000663.1:g.68910279A>C
NC_000001.9:g.68682867A>C
NG_008472.1:g.10364T>G
NG_008472.2:g.10364T>G
ENST00000262340.6:c.430T>G
ENST00000262340.5:c.430T>G
NM_000329.2:c.430T>G

Likely Pathogenic

Met criteria codes 5

PS3_Supporting | PM2_Supporting | PM3 | PP4 | 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.430T>G is a missense variant predicted to replace tyrosine with aspartic acid at position 144. This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 2.800e-7, with 2 alleles / 1180024 total alleles in the European (non-Finnish) population, 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 2 apparently unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 pt, PMID: 19117922, PMID: 11462243, PMID: 28127548, PM3). At least one proband harboring this variant exhibits a phenotype

including diagnosis of Leber congenital amaurosis (0.5 pts), reduced visual acuity (1 pt), macular atrophic changes (0.5 pts), abnormal electroretinogram responses, visual field constriction (1 pt), retinal vessel attenuation (0.5 pts), and retinal pigment epithelium depigmentation and granularity in the fundus (0.5 pts), which together are specific for RPE65-related recessive retinopathy (total 4 pts, PMID: 19117922, PP4). The computational predictor REVEL gives a score of 0.977, 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 no detectable enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD VCEP PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PMID: 16828753, PS3_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, PP3_Moderate, and PP4. (VCEP specifications version 1.0.0).

Met criteria codes

PS3_Supporting	✔	The variant exhibited no detectable enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD VCEP PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PMID: 16828753, PS3_Supporting).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 2.800e-7, with 2 alleles / 1180024 total alleles in the European (non-Finnish) population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PM3	✔	This variant has been reported in at least 2 apparently unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 pt, PMID: 19117922, PMID: 11462243, PMID: 28127548, PM3).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), reduced visual acuity (1 pt), macular atrophic changes (0.5 pts), abnormal ERG, visual field constriction (1 pt), vessel attenuation (0.5 pts), and RPE depigmentation and granularity in the fundus (0.5 pts), which together are specific for RPE65-related recessive retinopathy (total 4 pts, PMID: 19117922, PP4).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.977, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Curation History

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