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Variant: NM_000329.3(RPE65):c.143G>A (p.Gly48Glu)

Version: 1.1

CA340749160

1213912 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0ca3968d-db86-4bee-8808-9999cb0f019f
Approved on: 2026/8/20
Published on: 2026/8/20

HGVS expressions

NM_000329.3(RPE65):c.143G>A (p.Gly48Glu)
NM_000329.3:c.143G>A
NC_000001.11:g.68446812C>T
CM000663.2:g.68446812C>T
NC_000001.10:g.68912495C>T
CM000663.1:g.68912495C>T
NC_000001.9:g.68685083C>T
NG_008472.1:g.8148G>A
NG_008472.2:g.8148G>A
ENST00000262340.6:c.143G>A
ENST00000262340.5:c.143G>A
NM_000329.2:c.143G>A

Likely Pathogenic

Met criteria codes 5

PP3_Moderate | PP4 | PM3 | PM2_Supporting | PP1_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.143G>A (p.Gly48Glu) is a missense variant causing substitution of glycine with glutamic acid at position p.48. This variant is present in gnomAD v.4.1.1 at a total allele frequency of 6.19x10-7, with 1 allele / 1614088 total alleles in the total 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 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.859del variant confirmed in trans (PMID: 34492281), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total point,

PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset before age 1 year (1 pt), nystagmus (1 pt), night blindness with onset at age 1 year (0.5 pts), reduced visual fields (1 pt), reduced visual acuity (1 pt), diffuse retinal pigmentation, vascular thinning (0.5 pts), and optic disc pallor (0.5 pts), which together are specific for RPE65-related recessive retinopathy (6 total points, PMID: 34492281, PP4). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the compound heterozygous state (PP1_Moderate; PMID: 34492281). The computational predictor REVEL gives a score of 0.969, 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, PP1_moderate, PP3_Moderate, and PP4. (LCA/eoRD VCEP specifications version 1.0.0)

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.969, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset before age 1 year (1 pt), nystagmus (1 pt), night blindness with onset at age 1 year (0.5 pts), reduced visual fields (1 pt), reduced visual acuity (1 pt), diffuse retinal pigmentation, vascular thinning (0.5 pts), and optic disc pallor (0.5 pts), which together are specific for RPE65-related recessive retinopathy (6 total points, PMID: 34492281, PP4).
PM3	✔	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.859del variant confirmed in trans (PMID: 34492281), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PM3).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.1 at a total allele frequency of 6.19x10-7, with 1 allele / 1614088 total alleles in the total population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PP1_Moderate	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the compound heterozygous state (PP1_Moderate; PMID: 34492281).

Curation History

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