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# *Variant: NM_000329.3(RPE65):c.1451G>A (p.Gly484Asp)*

Version: 1.1

*CA226517*

*98848 (ClinVar)*

**Gene**: RPE65 (HGNC:6121)
**Condition**: RPE65-related recessive retinopathy (MONDO:0100368)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** b019b4c2-083e-4ca6-9a88-f11f9ca858c7
**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.1451G>A (p.Gly484Asp)**
**NM_000329.3:c.1451G>A**
NC_000001.11:g.68429927C>T
CM000663.2:g.68429927C>T
NC_000001.10:g.68895610C>T
CM000663.1:g.68895610C>T
NC_000001.9:g.68668198C>T
NG_008472.1:g.25033G>A
NG_008472.2:g.25033G>A
ENST00000262340.6:c.1451G>A
ENST00000262340.5:c.1451G>A
NM_000329.2:c.1451G>A

**Likely Pathogenic**

**Met criteria codes** 4

PP4_Moderate | PM2_Supporting | PM3 | PP3_Moderate

**Not Met criteria codes** 2

PM5 | PP1

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.1451G>A is a predicted missense variant substituting glycine by aspartic acid at position 484. The computational predictor REVEL gives a score of 0.984, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). Additionally, the splicing impact predictor SpliceAI gives a score of 0.23, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and predicts a damaging impact on splicing. This variant is present in gnomAD v.4.1.1 at a GroupMax allele frequency of 0.00000183, with 6 / 1179702 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 least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMID: 30025081, PM3). At least one proband harboring this variant exhibits a phenotype including congenital night blindness (0.5 pts), absent or severely decreased rod electroretinogram response (0.5 pts), abnormal cone ERG responses (1 pt), white dots on color photography in the context of severe retinal dysfunction (2 pts), poor pupillary light response (0.5 pts), pigmentary retinopathy with attenuated vessels (0.5 pts), decreased central visual acuity (1 pt), RPE mottling (0.5 pts), macular atrophy (0.5 pts), and symptomatic onset between birth and age five years (1 pt), which together are highly specific for RPE65-related recessive retinopathy (8 total points, PMID: 20811047, PP4_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, PP3_Moderate, and PP4_Moderate. (VCEP specifications version 1.0.0).**

**Met criteria codes**

| | | |
|---|---|---|
| **PP4_Moderate** | ✔ | At least one proband harboring this variant exhibits a phenotype including congenital night blindness (0.5 pt), absent or severely decreased rod electroretinogram response (0.5 pt), white dots on color photography in the context of severe retinal dysfunction (2 pt), poor pupillary light response (0.5 pt), pigmentary retinopathy with attenuated vessels (0.5 pt), decreased central visual acuity (1 pt), RPE mottling (0.5 pt), macular atrophy (0.5 pt), abnormal cone responses to 30 Hz flicker (1 pt) and symptomatic onset between birth and age five years (1 pt), which together are specific for RPE65-related recessive retinopathy (PMID: 20811047) [total 8 points, PP4_Moderate]. |
| **PM2_Supporting** | ✔ | This variant is present in gnomAD v.4.1.1 at a PopMax allele frequency of 0.00000183, with 6 / 1179702 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 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point(s), PMIDs: 30025081). (1 total point, PM3) |
| **PP3_Moderate** | ✔ | The computational predictor REVEL gives a score of 0.984, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). Additionally, the splicing impact predictor SpliceAI gives a score of 0.23, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and predicts a damaging impact on splicing. |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | Another missense variant in the same codon (NM_000329.3:c.1451G>T (p.Gly484Val)) was classified as pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PMID: 33472769). Splicing prediction using SpliceAI predicted an effect on splicing for both of these variants, with scores of 0.23 and 0.56 respectively for acceptor loss. Because these scores are not within 10% of each other, PM5 is not met. |
| **PP1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

Curation History

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