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# *Variant: NM_000329.3(RPE65):c.329A>G (p.Asp110Gly)*

Version: 1.0

*CA340748193*

*636202 (ClinVar)*

**Gene**: RPE65 (HGNC:6121)
**Condition**: RPE65-related recessive retinopathy (MONDO:0100368)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** d62d45f3-7072-4e35-a3dc-5a1e4ce58875
**Approved on**: 2024/7/23
**Published on**: 2024/7/23

## *HGVS expressions*

**NM_000329.3(RPE65):c.329A>G (p.Asp110Gly)**
**NM_000329.3:c.329A>G**
NC_000001.11:g.68444800T>C
CM000663.2:g.68444800T>C
NC_000001.10:g.68910483T>C
CM000663.1:g.68910483T>C
NC_000001.9:g.68683071T>C
NG_008472.1:g.10160A>G
NG_008472.2:g.10160A>G
ENST00000262340.6:c.329A>G
ENST00000262340.5:c.329A>G
NM_000329.2:c.329A>G

**Pathogenic**

**Met criteria codes** 5

PP3_Moderate | PP4 | PM1 | PM3_Strong | PM2_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 1.0.0*
- **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.329A>G (p.Asp110Gly) is a missense variant predicted to replace aspartic acid with glycine at position 110. This variant is a located within the membrane-interacting region between amino acids 107 and 125, which is a well-characterized functional domain required for proper localization to the ER membrane (PM1, PMID: 36265895). This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 0.0000007 with 4 alleles / 1180028 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). At least one proband harboring this variant exhibits**

**a phenotype including a diagnosis of Leber congenital amaurosis (0.5 pts), onset by age 2 years (1 pt), extinguished electroretinogram responses from both rods (0.5 pts) and cones (1 pt), nystagmus (1 pt), attenuated retinal vessels with bone spicule pigmentation (0.5 pts), and optic nerve atrophy (0.5 pts), which together are specific for RPE65-related recessive retinopathy (5 total points, PMID: 26626312, PP4). 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 point, PMID: 26626312). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.11+5G>A variant suspected in trans (0.5+0.5 points, PMID: 26626312), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong). The computational predictor REVEL gives a score of 0.945, 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 pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: PM1, PM2_Supporting, PM3_Strong, PP3_Moderate, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).**

**Met criteria codes**

| | | |
|---|---|---|
| **PP3_Moderate** | ✔ | The computational predictor REVEL gives a score of 0.945, 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 the diagnosis of LCA (0.5 pts), symptoms by age 2 (1 pt), extinct rod and cone ERGs (1.5 pts), nystagmus (1 pt), attenuated vessels with bone spicule pigmentation (0.5 pts), and atrophic optic nerve (0.5 pts). Previous genotyping with an LCA mutation panel was negative. Together these are specific for RPE65-related recessive retinopathy (5 total points, PMID: 26626312, PP4). |
| **PM1** | ✔ | This variant is a missense substitution within the membrane-interacting region between amino acids 107 and 125, which is a well-characterized functional domain required for proper localization to the ER membrane (PM1, PMID: 36265895). |
| **PM3_Strong** | ✔ | 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, PMID: 26626312). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the c.11+5G>A variant suspected in trans (0.5+0.5 points, PMID: 26626312), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong). |
| **PM2_Supporting** | ✔ | This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 7x10-7 with 4/ 1180028 alleles in the European (non-Finnish) population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). |

Curation History

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