

Variant: *NM_000329.3(RPE65):c.444G>T (p.Glu148Asp)*

Version: 1.0

CA226553 [↗](#)

98870 (ClinVar) [↗](#)

Gene: RPE65 ([HGNC:6121](#))

Condition: RPE65-related recessive retinopathy ([MONDO:0100368](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 0a7c6044-34a9-457f-bb90-23ec3c9b1836

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HGVS expressions

NM_000329.3(RPE65):c.444G>T (p.Glu148Asp)

NM_000329.3:c.444G>T

NC_000001.11:g.68444582C>A

CM000663.2:g.68444582C>A

NC_000001.10:g.68910265C>A

CM000663.1:g.68910265C>A

NC_000001.9:g.68682853C>A

NG_008472.1:g.10378G>T

NG_008472.2:g.10378G>T

ENST00000262340.6:c.444G>T

ENST00000262340.5:c.444G>T

NM_000329.2:c.444G>T

Likely Pathogenic

Met criteria codes **4**

PM3_Strong

PP1

PP3

PM2_Supporting

Not Met criteria codes **1**

PS3

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.444G>T (p.Glu148Asp) is a missense variant predicted to replace glutamate with aspartic acid at amino acid p.148. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 probands with early onset severe retinal dystrophy who harbored the variant in the compound heterozygous state, confirmed in trans with either the **NM_000329.3(RPE65):c.131G>A (p.Arg44Gln)** variant (PMID: 15024725), which been classified as pathogenic by the ClinGen LCA / eoRD VCEP, or with the **NM_000329.3(RPE65):c.1451G>A (p.Gly484Asp)** variant (PMID: 30268864), which has been classified as likely pathogenic

by the ClinGen LCA / eoRD VCEP (total 2 points, PM3_Strong). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 15024725, VCEP member-provided data). The computational predictor REVEL gives a score of 0.696, which is above the ClinGen LCA/eoRD VCEP threshold of ≥ 0.644 and predicts a damaging effect on RPE65 function (PP3). The splicing impact predictor SpliceAI gives a score of 0.06 for acceptor loss, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and does not strongly predict an impact on splicing. Introducing the equivalent Glu150Asp substitution into the SynACO enzyme (an ortholog from the unicellular bacterium Synechocystis) reduced its catalytic efficiency to $\sim 9\%$ of the wild-type enzyme (PMID: 34607013). However, PS3_Supporting is not met as this functional assay has not yet been approved by the ClinGen LCA / eoRD VCEP. 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_Strong, PP1, and PP3. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3_Strong			This variant has been reported in at least 2 probands with early onset severe retinal dystrophy who harbored the variant in the compound heterozygous state, confirmed in trans with either the NM_000329.3(RPE65):c.131G>A (p.Arg44Gln) variant (PMID: 15024725), which been classified as pathogenic by the ClinGen LCA / eoRD VCEP, or with the NM_000329.3(RPE65):c.1451G>A (p.Gly484Asp) variant (PMID: 30268864), which has been classified as likely pathogenic by the ClinGen LCA / eoRD VCEP (total 2 points, PM3_Strong).
PP1			The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 15024725, VCEP member-provided data).
PP3			The computational predictor REVEL gives a score of 0.696, which is above the ClinGen LCA/eoRD VCEP threshold of ≥ 0.644 and predicts a damaging effect on RPE65 function (PP3). The splicing impact predictor SpliceAI gives a score of 0.06 for acceptor loss, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and does not strongly predict an impact on splicing.
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS3			Introducing the equivalent Glu150Asp substitution into the SynACO enzyme (an ortholog from the unicellular bacterium Synechocystis) reduced its catalytic efficiency to $\sim 9\%$ of the wild-type enzyme (PMID: 34607013). PS3_Supporting is not met as this functional assay has not yet been approved by the ClinGen LCA / eoRD VCEP.
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Curation History 

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