

Variant: *NM_000329.3:c.762G>T*

Version: 1.0

CA902401 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: da68b3a7-7141-49bf-9316-0019694da3a8

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HGVS expressions

NM_000329.3:c.762G>T

NC_000001.11:g.68439287C>A

CM000663.2:g.68439287C>A

NC_000001.10:g.68904970C>A

CM000663.1:g.68904970C>A

NC_000001.9:g.68677558C>A

NG_008472.1:g.15673G>T

NG_008472.2:g.15673G>T

ENST00000262340.6:c.762G>T

ENST00000262340.5:c.762G>T

NM_000329.2:c.762G>T

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3_Moderate

PM2_Supporting

PM3

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

The NM_000329.3(RPE65):c.762G>T (p.Glu254Asp) variant is a missense variant in RPE65 causing a substitution of glutamic acid with aspartic acid at position 254. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.774, which is above the ClinGen LCA/eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). This variant has been reported in at least 3 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PM3, PMID: 35129589). At least one proband harboring this variant exhibits a phenotype including clinical diagnosis of LCA (0.5 pt) and significant, documented improvement of FST or other measure of dark-adapted vision after treatment

with Luxturna or other RPE65 gene therapy. (8.5 points, PMID: 38295874, 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, PP3_Moderate, PP4_Moderate, PM3 (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP4_Moderate			At least one proband harboring this variant exhibits a phenotype including clinical diagnosis of LCA (0.5 pt) and significant, documented improvement of FST or other measure of dark-adapted vision after treatment with Luxturna or other RPE65 gene therapy. (8.5 points, PMID: 38295874, PP4_Moderate).
PP3_Moderate			The computational predictor REVEL gives a score of 0.774, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM3			This variant has been reported in at least 3 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PM3, PMID: 35129589).

Curation History

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