The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000329.3(RPE65):c.859G>T (p.Val287Phe)

Version: 1.1

CA226585

98895 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8da5cb6f-1e37-44b9-9370-55c5637c4e64
Approved on: Tue, 22 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000329.3:c.859G>T
NM_000329.3(RPE65):c.859G>T (p.Val287Phe)
NC_000001.11:g.68439081C>A
CM000663.2:g.68439081C>A
NC_000001.10:g.68904764C>A
CM000663.1:g.68904764C>A
NC_000001.9:g.68677352C>A
NG_008472.1:g.15879G>T
NG_008472.2:g.15879G>T
ENST00000262340.6:c.859G>T
ENST00000262340.5:c.859G>T
NM_000329.2:c.859G>T

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM3_Strong PM2_Supporting PP3_Moderate

Not Met criteria codes 2

BP4 PM5

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.859G>T (p.Val287Phe) is both a missense variant, changing the valine at position 287 to phenylalanine, and a possible splicing variant, located at the first nucleotide of exon 9. SpliceAI's highest score is for Acceptor Loss, at 0.07, predicting a non-deleterious effect on splicing. The computational predictor REVEL has a score of 0.887, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.774 and predicts a damaging effect on RPE65 function (PP3_moderate). This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00001426, with 4 alleles / 1613770 total alleles in the South Asian 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 diagnosis of LCA (0.5 pts) and significant improvement after gene therapy treatment (8 pts), which together are highly specific for RPE65-related recessive retinopathy (8.5 points, PMID: 21911650 , PP4_Moderate). 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, PMIDs: 18722466, 21911650). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.938A>G (p.His313Arg) variant confirmed in trans (1 point, VCEP member-provided data), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). 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: PP3_Moderate, PM2_Supporting, PP4_Moderate, and PM3_Strong. (VCEP specifications version 1.0.0)

Met criteria codes

PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts), and significant improvement after gene therapy treatment (8 pts), which together are highly specific for RPE65-related recessive retinopathy (8.5 points, PMID: 21911650 , PP4_Moderate).
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, PMIDs: 18722466, 21911650). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.938A>G (p.His313Arg) variant confirmed in trans (1 point, VCEP member-provided data), 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.4.1.1 at a GrpMax allele frequency of 0.00001426, with 4 alleles / 1613770 total alleles in the South Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.887, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Not Met criteria codes

BP4	✖	Mutation site is the first nucleotide of exon 9. SpliceAI highest score is for Acceptor Loss at 0.07, predicting a non-deleterious effect on splicing. However, the computational predictor REVEL gives a score of 0.887, which is above the ClinGen LCA / eoRD VCEP threshold of <0.290 and does not predict a non-damaging effect on RPE65 function.
PM5	✖	At the time of review, there were no variants at this amino acid residue reported in ClinVar (January 2024).

Curation History

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