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

Version: 1.0

CA523302413

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9e5e00db-a323-429a-9532-94b659842f88
Approved on: 2025-03-27
Published on: 2025-03-27

HGVS expressions

NM_000329.3:c.106del
NC_000001.11:g.68446853del
CM000663.2:g.68446853del
NC_000001.10:g.68912536del
CM000663.1:g.68912536del
NC_000001.9:g.68685124del
NG_008472.1:g.8111del
NG_008472.2:g.8111del
ENST00000262340.6:c.106del
ENST00000262340.5:c.106del
NM_000329.2:c.106del

Pathogenic

Met criteria codes 5

PM3 PP4_Moderate PVS1 PM2_Supporting 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 1.0.0*
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.106del (p.Leu36SerfsTer?) variant introduces a premature stop codon into exon 3 of 14, and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1). This variant is present in gnomAD v.4.1.0 at an allele frequency of 8.474e-7 , with 1 allele / 1180032 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 at least 1 proband with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state (confirmed in trans) with a Pathogenic variant previously classified by the LCA/eoRD VCEP (1 pt, PM3)(PMID: 33308271). At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) with nystagmus (1 pt), myopia, retinal degeneration at 2-years-old (1 pt), sluggish pupillary responses (0.5 pts), extensive atrophic retinal changes, salt and pepper fundus appearance (2 pts), optic disc pallor, and extinguished rod and cone ERG (1.5 pts). Screening by NGS did not reveal any additional variants of interest (2 pts). Together

these phenotypes are highly specific for RPE65-related recessive retinopathy (total 8.5 points, PMID: 33308271, PP4_Moderate).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: 33308271).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: PVS1, PM2_supporting, PP4_moderate, PP1, PM3. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state (confirmed in trans) with a Pathogenic variant previously classified by the LCA/eoRD VCEP (1 pt, PM3)(PMID: 33308271).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) with nystagmus (1 pt), myopia, retinal degeneration at 2-years-old (1 pt), sluggish pupillary responses (0.5 pts), extensive atrophic retinal changes, salt and pepper fundus appearance (2 pts), optic disc pallor, and extinguished rod and cone ERG (1.5 pts). Screening by NGS did not reveal any additional variants of interest (2 pts). Together these phenotypes are highly specific for RPE65-related recessive retinopathy (total 8.5 points, PMID: 33308271, PP4_Moderate).
PVS1	✔	This is a frameshift variant that introduces a premature stop codon into exon 3 of 14, and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at an allele frequency of 8.474e-7 , with 1 allele / 1180032 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).
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: 33308271).

Curation History

Showing 1 to 1 of 1 rows