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.55G>A (p.Val19Met)

Version: 1.1

CA340750220

2944236 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7561359c-6530-4b00-a818-405ac597d9da
Approved on: Tue, 22 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000329.3:c.55G>A
NM_000329.3(RPE65):c.55G>A (p.Val19Met)
NC_000001.11:g.68448663C>T
CM000663.2:g.68448663C>T
NC_000001.10:g.68914346C>T
CM000663.1:g.68914346C>T
NC_000001.9:g.68686934C>T
NG_008472.1:g.6297G>A
NG_008472.2:g.6297G>A
ENST00000262340.6:c.55G>A
ENST00000262340.5:c.55G>A
NM_000329.2:c.55G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP1 PM3 PP4_Moderate

Not Met criteria codes 1

PP3

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

The NM_000329.3(RPE65):c.55G>A (p.Val19Met) missense variant is predicted to replace the valine at position 19 with methionine. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including congenital night blindness (0.5 pts) , decreased rod responses on ERG (0.5 pts), large gene panel testing without other significant findings (2 pts) , hypoautofluorescence (2 pts), optic nerve pallor (0.5 pts), pigmentary retinopathy (0.5 pts), posterior subcapsular cataract (0.5 pts), RPE mottling (0.5.pts), partial macular atrophy (0.5 pts), symptomatic onset before age 5 (1 pt), OCT preserved with respect to vision

loss (1 pt), decreased peripheral vision (1 pt), ERG demonstrated cone involvement (1 pt), and decreased central visual acuity (1 pt) which together are highly specific for RPE65-related recessive retinopathy (total 12.5 points, PP4_Moderate).This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.65T>C (p.Leu22Pro) confirmed in trans (1 point) which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1.0 total points, PM3). 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).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, PP4_Moderate, PM3, PP1. (VCEP specifications version 1.0.0.)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (PM2_Supporting).
PP1	✔	Patient has similarly affected sister who has been genotyped and is heterozygous for both the p.Val19Met and p.Leu22Pro variants.
PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.65T>C (p.Leu22Pro) confirmed in trans (1 point) which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1.0 total points, PM3).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including congenital night blindness (0.5 pts) , decreased rod responses on ERG (0.5 pts), large gene panel testing (2 pts) , hypoautofluorescence (2 pts), optic nerve pallor (0.5 pts), pigmentary retinopathy (0.5 pts), posterior subcapsular cataract (0.5 pts), RPE mottling (0.5.pts), partial macular atrophy (0.5 pts), symptomatic onset before age 5 (1 pt), OCT preserved with respect to vision loss (1 pt), decreased peripheral vision (1 pt), ERG demonstrated cone involvement (1 pt), and decreased central visual acuity (1 pt) which together are highly specific for RPE65-related recessive retinopathy (total 12.5 points, PP4_Moderate).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.553, which is below the ClinGen LCA/eoRD VCEP threshold of ≥0.644 and does not predict a damaging effect on RPE65 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.

Curation History

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