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Variant: NM_000329.3(RPE65):c.65T>C (p.Leu22Pro)

Version: 2.0

CA226576

98888 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: c08da84b-5627-46e5-af56-e4e3c3ee7130
Approved on: Tue, 22 Sep 2026 00:00:00 +0000
Published on: Tue, 22 Sep 2026 00:00:00 +0000

HGVS expressions

NM_000329.3(RPE65):c.65T>C (p.Leu22Pro)
NM_000329.3:c.65T>C
NC_000001.11:g.68448653A>G
CM000663.2:g.68448653A>G
NC_000001.10:g.68914336A>G
CM000663.1:g.68914336A>G
NC_000001.9:g.68686924A>G
NG_008472.1:g.6307T>C
NG_008472.2:g.6307T>C
ENST00000262340.6:c.65T>C
ENST00000262340.5:c.65T>C
NM_000329.2:c.65T>C

Pathogenic

Met criteria codes 5

PP4_Moderate | PP3 | PS3_Supporting | PM3_Very Strong | PM2_Supporting

Not Met criteria codes 2

BA1 | BS1

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.65T>C is a missense variant causing substitution of leucine with proline at position 22. This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00006679, with 5 alleles/74866 total alleles in the African/African American 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 onset in infancy (1 pt), nyctalopia since childhood (0.5 pts), diagnosis based on a 300-gene testing panel that did not provide an alternative explanation for visual impairment (2 pts), non-detectable rod ERG response (0.5 pts),

reduced cone ERG response (1 pt), reduced visual acuity (1 pt), light-seeking behavior (1 pt), retinal vessel attenuation (0.5 pts), optic nerve pallor (0.5 pts), and pigment clumping (0.5 pts), which together are highly specific for RPE65-related recessive retinopathy (8 total points, VCEP member-provided data, PP4_Moderate). This variant has been reported in 2 probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 pt, PMIDs: 35129589, 28127548, 38002999, VCEP member-provided data). This variant has also been reported in 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65): c.893delA (p.Lys298fs) variant, which was previously classified as pathogenic by the ClinGen LCA / eoRD VCEP, confirmed in trans (1 pt, Personal communication). This variant has also been reported in 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.1067dup (p.Asn356fs) or NM_000329.3(RPE65):c.10C>T (p.Gln4Ter) variants which were previously classified as pathogenic by the ClinGen LCA / eoRD VCEP suspected in trans (1 pt, PMID: 35129589, PMID:32865313). This variant was reported in 1 proband with early-onset retinal dystrophy who was compound heterozygous with NM_000329.3(RPE65):c.1249G>C (p.Glu417Gln) which was previously classified as likely pathogenic confirmed in trans (1 pt, PMID:38002999). This variant was reported in 1 proband with early-onset retinal dystrophy who was compound heterozygous with NM_000329.3(RPE65):c.272G>C (p.Arg91Pro) which was previously classified as likely pathogenic suspected in trans (0.25 pts, PMID:38002999). This variant was reported in 1 proband with retinitis pigmentosa who was a compound heterozygote with the NM_000329.3:c.201_202delinsTT (p.His68Tyr) variant, which is classified as a variant of unknown significance, confirmed in trans (PMID: 9801879, PMID: 11264131). The variant is confirmed in trans with the NM_000329.3(RPE65):c.208T>G (p.Phe70Val) variant which was previously classified as likely pathogenic (PMID: 17724218) but wasn't counted to avoid circularity. (4.25 total pts, PM3_Very Strong). The computational predictor REVEL gives a score of 0.711, which is above the ClinGen LCA / eoRD VCEP PP3 threshold of ≥0.644 and predicts a damaging effect on RPE65 function (PP3). The variant exhibited 2.8-13.5% enzymatic activity in retinoid isomerase assays relative to the wild-type control, which is lower than the ClinGen LCA / eoRD PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, PMID: 18599565, PMID: 24849605, PMID: 26427455). 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: PS3_Supporting, PM2_Supporting, PM3_Very Strong, PP3, and PP4_Moderate. (VCEP specifications version 1.0.0)

Met criteria codes

PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including onset in infancy (1 pt), nyctalopia since childhood (0.5 pts), diagnosis based on a 300-gene testing panel that did not provide an alternative explanation for visual impairment (2 pts), non-detectable rod ERG response (0.5 pts), reduced cone ERG response (1 pt), reduced visual acuity (1 pt), light-seeking behavior (1 pt), retinal vessel attenuation (0.5 pts) optic nerve pallor (0.5 pts), and pigment clumping (0.5 pts), which together are highly specific for RPE65-related recessive retinopathy (8 total points, VCEP member-provided data, PP4_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.711, which is above the ClinGen LCA/eoRD VCEP PP3 threshold of ≥0.644 and predicts a damaging effect on RPE65 function (PP3). The splicing impact predictor SpliceAI gives a score of 0.00, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PS3_Supporting	✔	The variant exhibited 2.8-13.5 % enzymatic activity in retinoid isomerase assays relative to the wild-type control, which is lower than the ClinGen LCA / eoRD PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, PMID: 18599565, PMID: 24849605, PMID: 26427455).
PM3_Very Strong	✔	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who was homozygous for the variant (1.0 pt, PMIDs: 35129589, 28127548, 38002999, VCEP member-provided data). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65): c.893delA (p.Lys298fs) variant which were previously classified as pathogenic by the ClinGen LCA / eoRD VCEP confirmed in trans (1.0pt, Personal communication). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.1067dup (p.Asn356fs) or NM_000329.3(RPE65):c.10C>T (p.Gln4Ter)

variants which were previously classified as pathogenic by the ClinGen LCA / eoRD VCEP suspected in trans (1.0pt, PMID: 35129589, PMID:32865313). This variant was reported in at least 1 proband with early-onset retinal dystrophy who were compound heterozygotes with NM_000329.3(RPE65):c.1249G>C (p.Glu417Gln) which was previously classified as likely pathogenic confirmed in trans (1pts, PMID:38002999). This variant was reported in at least 1 proband with early-onset retinal dystrophy who was compound heterozygotes with NM_000329.3(RPE65):c.272G>C (p.Arg91Pro) which was previously classified as likely pathogenic suspected in trans (0.25pts, PMID:38002999). This variant was reported in at least 1 proband with retinitis pigmentosa who was a compound heterozygote with the NM_000329.3:c.201_202delinsTT (p.His68Tyr) variant which is classified as a variant of unknown significance confirmed in trans (PMID: 9801879, PMID: 11264131). The variant is confirmed in trans with the NM_000329.3(RPE65):c.208T>G (p.Phe70Val) variant which was previously classified as likely pathogenic (PMID: 17724218) but wasn't counted to avoid circularity. (4.25 total pts, PM3_Very Strong).

PM2_Supporting ✔

This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00006679, with 5 alleles/74866 total alleles] in the African/African American population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).

Not Met criteria codes

BA1 ✖

The Popmax Filtering AF for this variant in gnomAD v.2.1.1 is 0.00002137. This allele frequency is lower than the ClinGen LCA/eoRD VCEP threshold (>0.00816) for this criterion.

BS1 ✖

The Popmax Filtering AF for this variant in gnomAD v.2.1.1 is 0.00002137. This allele frequency is lower than the ClinGen LCA/eoRD VCEP threshold (>0.000816) for this criterion.

Curation History

Showing 1 to 2 of 2 rows

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