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Variant: NM_000329.3(RPE65):c.215T>C (p.Phe72Ser)

Version: 1.0

CA340748948

467826 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: b4b83bc1-846d-4f9b-90e8-c75a6baffc80
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:c.215T>C
NM_000329.3(RPE65):c.215T>C (p.Phe72Ser)
NC_000001.11:g.68446740A>G
CM000663.2:g.68446740A>G
NC_000001.10:g.68912423A>G
CM000663.1:g.68912423A>G
NC_000001.9:g.68685011A>G
NG_008472.1:g.8220T>C
NG_008472.2:g.8220T>C
ENST00000262340.6:c.215T>C
ENST00000262340.5:c.215T>C
NM_000329.2:c.215T>C

Pathogenic

Met criteria codes 5

PP4_Moderate PM3_Strong PM2_Supporting PP1 PP3_Moderate

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.215T>C (p.Phe72Ser) is a missense variant that replaces phenylalanine with serine at amino acid 72. This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.000009530, with 18 alleles / 1180044 total alleles in the non-Finnish European 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 2 unrelated probands with early-onset severe retinal dystrophy who carry the NM_000329.2:c.130C>T, p.Arg44* variant, confirmed in trans, which was previously classified as pathogenic by the ClinGen LCA/eoRD VCEP. (2.0 points, VCEP member and

clinical lab testing results). This variant has also been reported in at least 1 proband and a sibling with early-onset severe retinal dystrophy who are compound heterozygous, phase unknown, with the NM_000329.2:c.617T>C, p.Ile206Thr variant, previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (0.25 points, VCEP member clinical lab testing results), (2.25 total points, PM3_Strong). At least one proband harboring this variant exhibits a phenotype including: absent or severely decreased rod electroretinogram (ERG) responses (0.5 pts), congenital night blindness/nyctalopia (0.5 pts), clinical diagnosis of early onset Rod Cone Dystrophy (0.5 pts), previous retinal dystrophy gene panel testing that did not provide an alternative explanation for visual impairment (2 pts), pigmentary retinopathy with attenuated vessels (0.5 pts), RPE mottling (0.5 pts), symptomatic onset between birth and five years (1 pt), OCT is preserved with respect to vision loss (1 pt), decreased peripheral vision (1 pt), abnormal color vision or evidence of cone involvement on ERG (1 pt), and decreased central visual acuity (1 pt), which together are highly specific for RPE65-related recessive retinopathy (9.5 points in total, unpublished clinical observation, 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 (unpublished clinical evidence, PP1). The computational predictor REVEL gives a score of 0.946, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on RPE65 function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.01, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. 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: PM2_Supporting, PM3_Strong, PP4_Moderate, PP1, PP3_Moderate. (VCEP specifications version 1.0.0).

Met criteria codes

PP4_Moderate ✔	At least one proband harboring this variant exhibits a phenotype including: absent or severely decreased rod electroretinogram (ERG) responses (0.5 pts), congenital night blindness/nyctalopia (0.5 pts), clinical diagnosis of early onset Rod Cone Dystrophy (0.5 pts), previous retinal dystrophy gene panel testing that did not provide an alternative explanation for visual impairment (2 pts), pigmentary retinopathy with attenuated vessels (0.5 pts), RPE mottling (0.5 pts), symptomatic onset between birth and five years (1 pt), OCT is preserved with respect to vision loss (1 pt), decreased peripheral vision (1 pt), abnormal color vision or evidence of cone involvement on ERG (1 pt), and decreased central visual acuity (1 pt), which together are highly specific for RPE65-related recessive retinopathy (9.5 points in total, unpublished clinical observation, PP4_Moderate).
PM3_Strong ✔	This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who are compound heterozygous in trans with the NM_000329.3:c.130C>T, p.Arg44* variant, which was previously classified as pathogenic by the ClinGen LCA/eoRD VCEP. (2.0 points, VCEP member and clinical lab testing results). This variant has been reported in at least 1 proband and a sibling with early-onset severe retinal dystrophy who are compound heterozygous, phase unknown, with the NM_000329.3:c.617T>C, p.Ile206Thr variant, which was previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (0.25 points, VCEP member clinical lab testing results). The variant is also reported in at least 1 unrelated proband with early-onset severe retinal dystrophy who is compound heterozygous with the NM_000329.3:c.308T>C. Phe103Ser, currently a variant of uncertain significance. This variant will not count in this curation so that Phe72Ser can be used to curate Phe103Ser and avoid circularity (0 points) (2.25 total points, PM3_strong).
PM2_Supporting ✔	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.000009530, with 18 alleles / 1180044 total alleles in the non-Finnish European 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; Clinical evidence).
PP3_Moderate ✔	The computational predictor REVEL gives a score of 0.946, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on RPE65 function. The splicing impact predictor SpliceAI gives a score of

0.01, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing (PP3_Moderate).

Curation History

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