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Variant: NM_000329.3(RPE65):c.755T>C (p.Phe252Ser)

Version: 1.1

CA340745829

556104 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6bae432c-d50d-40d9-b150-a7e15d26fa0e
Approved on: 2026/8/20
Published on: 2026/8/20

HGVS expressions

NM_000329.3(RPE65):c.755T>C (p.Phe252Ser)
NM_000329.3:c.755T>C
NC_000001.11:g.68439294A>G
CM000663.2:g.68439294A>G
NC_000001.10:g.68904977A>G
CM000663.1:g.68904977A>G
NC_000001.9:g.68677565A>G
NG_008472.1:g.15666T>C
NG_008472.2:g.15666T>C
ENST00000262340.6:c.755T>C
ENST00000262340.5:c.755T>C
NM_000329.2:c.755T>C

Likely Pathogenic

Met criteria codes 5

PP1 PP4 PM3 PP3_Moderate PM2_Supporting

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.755T>C (p.Phe252Ser) is a missense variant in exon 8 of 14, changing the phenylalanine at position 252 to serine. This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00000068, with 3 / 1179970 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). The computational predictor REVEL gives a score of 0.986, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on RPE65 function (PP3_Moderate). This variant has been reported in at least 1 proband with early-onset severe retinal

dystrophy who is compound heterozygous with the NM_000329.3(RPE65):c.1360del (p.Thr454LeufsTer?) variant confirmed in trans (1 point, PMID:28130426), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PM3). NM_000329.3(RPE65):c.755T>C (p.Phe252Ser) 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: 28130426). At least one proband (RF.T.111, patient II-I) harboring this variant exhibits a phenotype including severely decreased ERG responses (0.5 pt), optic disc pallor (0.5pt), pigmentary retinopathy with attenuated vessels (0.5 pt), symptomatic onset between birth an age five years (1 pt), decreased peripheral vision (1 pt), abnormal color vision (1 pt), decreased central visual acuity (1 pt), and nystagmus (1 pt), which together are specific for RPE65-related recessive retinopathy (6.5 points, PMID: 28130426, PP4). 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, PM3, PP1, PP3_moderate, and PP4. (VCEP specifications version 1.0.0).

Met criteria codes

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: 28130426).
PP4	✔	At least one proband (RF.T.111, patient II-I) harboring this variant exhibits a phenotype including severely decrease ERG responses (0.5), optic disc pallor (0.5), pigmentary retinopathy with attenuated vessels (0.5), symptomatic onset between birth an age five years (1), decreased peripheral vision (1), abnormal color vision (1), decreased central visual acuity (1), and nystagmus (1), which together are specific for RPE65-related recessive retinopathy (6.5 points, PMID: 28130426, PP4).
PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who is compound heterozygous with the NM_000329.3(RPE65):c.1360del (p.Thr454LeufsTer?) variant confirmed in trans (1 point, PMIDs:28130426), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PM3).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.986, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00000068, with 3 / 1179970 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).

Curation History

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