

Variant: *NM_000329.3(RPE65):c.1409C>T (p.Pro470Leu)*

Version: 1.0

CA340741897 [↗](#)

1070754 (ClinVar) [↗](#)

Gene: RPE65 ([HGNC:6121](#))

Condition: RPE65-related recessive retinopathy ([MONDO:0100368](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: d2f373ab-d7e0-4068-ab9a-181bd66c86a1

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HGVS expressions

NM_000329.3:c.1409C>T

NM_000329.3(RPE65):c.1409C>T (p.Pro470Leu)

NC_000001.11:g.68431106G>A

CM000663.2:g.68431106G>A

NC_000001.10:g.68896789G>A

CM000663.1:g.68896789G>A

NC_000001.9:g.68669377G>A

NG_008472.1:g.23854C>T

NG_008472.2:g.23854C>T

ENST00000262340.6:c.1409C>T

ENST00000262340.5:c.1409C>T

NM_000329.2:c.1409C>T

Likely Pathogenic

Met criteria codes **5**

PP3_Moderate

PP1_Moderate

PM2_Supporting

PP4

PM3

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

NM_000329.3(RPE65):c.1409C>T (p.Pro470Leu) is a missense variant causing substitution of proline with leucine at amino acid 470. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.0000006, with 1 allele of 1,613,736 total alleles, 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 0.966, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The splicing impact predictor SpliceAI gives scores of 0.01 for donor loss and acceptor gain, which are below the ClinGen LCA / eoRD VCEP

recommended threshold of ≥ 0.2 and do not strongly predict an impact on splicing. This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMID: 26147992, PMID: 18484312, PM3). At least one proband harboring this variant exhibits a phenotype including absent rod electroretinogram (ERG) responses (0.5 pts), white/yellow dots on color photography of the type seen in fundus albipunctatus in the context of severe retinal dysfunction (2 pts), attenuated vessels (0.5 pts), and nystagmus (1 pt), which together are specific for RPE65-related recessive retinopathy (4 points, PMID: 26147992, 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, PP3_Moderate, PM3, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP3_Moderate			The computational predictor REVEL gives a score of 0.966, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The splicing impact predictor SpliceAI gives scores of 0.01 for donor loss and acceptor gain, which are below the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and do not strongly predict an impact on splicing.
PP1_Moderate			The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PP1_Moderate; PMID: 26147992).
PM2_Supporting			This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.0000006, with 1 allele of 1,613,736 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of < 0.0002 (PM2_Supporting).
PP4			At least one proband harboring this variant exhibits a phenotype including absent rod electroretinogram (ERG) responses (0.5), white/yellow dots on color photography of the type seen in fundus albipunctatus in the context of severe retinal dysfunction (2), attenuated vessels (0.5), and nystagmus (1), which together are specific for RPE65-related recessive retinopathy (4 points, PMID: 26147992, PP4).
PM3			This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMID: 26147992, PMID: 18484312, PM3).

Curation History

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