

Variant: NM_000329.3(RPE65):c.1078G>C (p.Ala360Pro)

Version: 1.0

CA226480 [↗](#)

98823 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9ee1484f-82bf-4018-ae20-2f7ca818ed01

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HGVS expressions

NM_000329.3:c.1078G>C

NM_000329.3(RPE65):c.1078G>C (p.Ala360Pro)

NC_000001.11:g.68438237C>G

CM000663.2:g.68438237C>G

NC_000001.10:g.68903920C>G

CM000663.1:g.68903920C>G

NC_000001.9:g.68676508C>G

NG_008472.1:g.16723G>C

NG_008472.2:g.16723G>C

ENST00000262340.6:c.1078G>C

ENST00000262340.5:c.1078G>C

NM_000329.2:c.1078G>C

Likely Pathogenic

Met criteria codes **4**

PM2_Supporting

PP3

PP4

PM3_Strong

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.1078G>C is a missense variant predicted to replace alanine with proline at position 360. This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 0.000001240, with 5 alleles / 1179942 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). This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.1282_1303del (p.Gly428MetfsTer5) or NM_000329.3(RPE65):c.1039C>T (p.Arg347Cys) variants confirmed in trans

(PMID: 19431183, PMID: 33952291), both were previously classified likely pathogenic by the ClinGen LCA/eoRD VCEP (2 points total, PM3_strong). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) by next-generation sequencing-based genotyping of a panel of 586 eye disease-associated genes (2 pts), congenital onset (1 pt), reduced central visual acuity (1 pt), extinct ERG responses from rods (0.5 pts) and cones (1 pt), and nystagmus (1 pt), which together are specific for RPE65-related recessive retinopathy (7 pts total, PMID: 33952291, PP4). The computational predictor REVEL gives a score of 0.677, which is above the ClinGen LCA/eoRD VCEP threshold of ≥ 0.644 and predicts a damaging effect on RPE65 function (PP3). 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_Strong, PP3, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM2_Supporting			This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 0.000001240, with 5 alleles / 1179942 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).
PP3			The computational predictor REVEL gives a score of 0.677, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.644 and predicts a damaging effect on RPE65 function (PP3).
PP4			At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) by next-generation sequencing-based genotyping of a panel of 586 eye disease-associated genes (2 pts), congenital onset (1 pt), reduced central visual acuity (1 pt), extinct ERG responses from rods (0.5 pts) and cones (1 pt), and nystagmus (1 pt), which together are specific for RPE65-related recessive retinopathy (7 pts total, PMID: 33952291, PP4).
PM3_Strong			This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.1282_1303del (p.Gly428MetfsTer5) or NM_000329.3(RPE65):c.1039C>T (p.Arg347Cys) variants confirmed in trans (PMID: 19431183, PMID: 33952291), both were previously classified likely pathogenic by the ClinGen LCA / eoRD VCEP (2 points total, PM3_strong). This variant has been reported in at least 1 proband with a diagnosis of retinitis pigmentosa who harbored the variant in the homozygous state (PMID: 25097241). However, the proband was not counted for PM3 because sufficient phenotype details to establish severity were unavailable.

Curation History



 

 

Showing 1 to 1 of 1 rows

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