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Variant: NM_000329.3(RPE65):c.272G>C (p.Arg91Pro)

Version: 1.0

CA226534

98858 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 11504136-283d-4ad2-854a-0cf6a92d1f2b
Approved on: 2025/6/11
Published on: 2025/6/11

HGVS expressions

NM_000329.3(RPE65):c.272G>C (p.Arg91Pro)
NM_000329.3:c.272G>C
NC_000001.11:g.68444857C>G
CM000663.2:g.68444857C>G
NC_000001.10:g.68910540C>G
CM000663.1:g.68910540C>G
NC_000001.9:g.68683128C>G
NG_008472.1:g.10103G>C
NG_008472.2:g.10103G>C
ENST00000262340.6:c.272G>C
ENST00000262340.5:c.272G>C
NM_000329.2:c.272G>C

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PP3 PM1 PM3 PM2_Supporting

Not Met criteria codes 1

PM5

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.272G>C (p.Arg91Pro) is a missense variant predicted to replace arginine with proline at amino acid p.91. This residue is a well-characterized functional site that forms a salt bridge with glutamate 127 that is reportedly required for correct positioning of membrane-binding elements that mediate localization to the ER membrane (PMID: 19805034, PM1). Another missense variant in the same codon, NM_000329.3(RPE65):c.272G>A (p.Arg91Gln), has been classified as pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP. However, splicing prediction using SpliceAI indicated a likely splicing defect due to

NM_000329.3(RPE65):c.272G>A (p.Arg91Gln) (score of 0.21 for acceptor loss) that was not predicted for the present variant (with a score of 0.12 for acceptor gain), so the PM5 code was not met. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.430T>G (p.Tyr144Asp) variant confirmed in trans (1 point, PMID: 17724218) which was previously classified likely pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PM3). The variant has also been reported in a second proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.65T>C (p.Leu22Pro) variant suspected in trans (PMID: 32865313), which was not included in the PM3 code. At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), light-gazing (1 pt), visual acuity limited to light perception (1 pt), nystagmus (1 pt), extinguished ERG responses from both rods (0.5 pts) and cones (1 pt), salt-and-pepper fundus (0.5 pts) with macular atrophy (0.5 pts), and absence of fundus autofluorescence (2 pts), which together are highly specific for RPE65-related recessive retinopathy (total 8 points, PMID: 17724218, PP4_Moderate). The computational predictor REVEL gives a score of 0.766, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and predicts a damaging effect on RPE65 function (PP3). The splicing impact predictor SpliceAI gives a score of 0.12 for acceptor gain, 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 likely pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM1, PM2_Supporting, PM3, PP3, and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), light-gazing (1 pt), visual acuity limited to light perception (1 pt), nystagmus (1 pt), extinguished ERG responses from both rods (0.5 pts) and cones (1 pt), salt-and-pepper fundus (0.5 pts) with macular atrophy (0.5 pts), and absence of fundus autofluorescence (2 pts), which together are highly specific for RPE65-related recessive retinopathy (total 8 points, PMID: 17724218, PP4_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.766, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and predicts a damaging effect on RPE65 function (PP3). The splicing impact predictor SpliceAI gives a score of 0.12 for acceptor gain, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM1	✔	This variant is a missense substitution at residue 91, which is a well-characterized functional site that forms a salt bridge with glutamate 127 that is reportedly required for correct positioning of membrane-binding elements that mediate localization to the ER membrane (PMID: 19805034, PM1).
PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.430T>G (p.Tyr144Asp) variant confirmed in trans (1 point, PMID: 17724218) which was previously classified likely pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PM3). The variant has also been reported in a second proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.65T>C (p.Leu22Pro) variant suspected in trans (PMID: 32865313), which was not included in the PM3 code.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM5	✖	Another missense variant in the same codon, NM_000329.3(RPE65):c.272G>A (p.Arg91Gln), has been classified as pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP. However, splicing prediction using SpliceAI indicated a likely splicing defect due to NM_000329.3(RPE65):c.272G>A (p.Arg91Gln) (score of 0.21

for acceptor loss) that was not predicted for the present variant (with a score of 0.12 for acceptor gain), so the PM5 code was not met.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000329.3(RPE65):c.272G>C (p.Arg...	Likely Pathogenic	RPE65-Related Recessive Retinopathy	2025-06-11	1.0	ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RPE65 Version 1.0.0	RPE65

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