The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000329.3(RPE65):c.124C>T (p.Leu42Phe)

Version: 1.0

CA902590

968598 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 26b97ce6-22c1-4a53-8b84-cb27cf96c2b0
Approved on: 2024/12/12
Published on: 2024/12/12

HGVS expressions

NM_000329.3(RPE65):c.124C>T (p.Leu42Phe)
NM_000329.3:c.124C>T
NC_000001.11:g.68446831G>A
CM000663.2:g.68446831G>A
NC_000001.10:g.68912514G>A
CM000663.1:g.68912514G>A
NC_000001.9:g.68685102G>A
NG_008472.1:g.8129C>T
NG_008472.2:g.8129C>T
ENST00000262340.6:c.124C>T
ENST00000262340.5:c.124C>T
NM_000329.2:c.124C>T

Likely Pathogenic

Met criteria codes 4

PM3 PP3_Moderate PP4 PM2_Supporting

Not Met criteria codes 1

PS3

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.124C>T is a missense variant that replaces leucine with phenylalanine at position 42. This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 0.00003588, with 7 alleles / 91068 total alleles in the South Asian 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 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.130C>T (p.Arg44Ter) variant (PMID: 30996589) or the NM_000329.3(RPE65):c.495+1dup variant (VCEP member-provided data) suspected in trans,

both of which were previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset in the first few months of life (1 pt), genotyping by targeted exome sequencing focused on 194 IRD genes without identifying an alternative basis for disease (2 points), poor vision limited to hand movement (1 pt), nystagmus (1 pt), maculopathy (0.5 pts), peripheral hyperpigmentation, and retinal vascular attenuation (0.5 pts), which together are specific for RPE65-related recessive retinopathy (total 6.5 points, PMID: 30996589, PP4). The computational predictor REVEL gives a score of 0.879, 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 a score of 0.01 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. A molecular dynamics and simulation-based model of the variant predicts that the variant would destabilize the structure of RPE65 (PMID: 32072079). However, this is not currently an approved form of functional evidence, so the PS3_Supporting code is not met. 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, PP3_Moderate, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3	✔	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.130C>T (p.Arg44Ter) variant (PMID: 30996589) or the NM_000329.3(RPE65):c.495+1dup variant (VCEP member-provided data) suspected in trans, both of which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PM3).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.879, 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 a score of 0.01 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.
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset in the first few months of life (1 pt), genotyping by targeted exome sequencing focused on 194 IRD genes without identifying an alternative basis for disease (2 points), poor vision limited to hand movement (1 pt), nystagmus (1 pt), maculopathy (0.5 pts), peripheral hyperpigmentation, and retinal vascular attenuation (0.5 pts), which together are specific for RPE65-related recessive retinopathy (total 6.5 points, PMID: 30996589, PP4).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.00003588, with 7 alleles / 91068 total alleles in the South Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).

Not Met criteria codes

PS3	✖	A molecular dynamics and simulation-based model of the variant predicts that the variant would destabilize the structure of RPE65 (PMID: 32072079). However, this is not currently an approved form of functional evidence, so the PS3_Supporting code is not met.

Curation History

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