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Variant: NM_000329.3(RPE65):c.1597T>A (p.Ser533Thr)

Version: 1.0

CA902125

870342 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 735c5a86-d4d4-43c1-9cd2-06280c74846e
Approved on: 2024-02-18
Published on: 2024-02-18

HGVS expressions

NM_000329.3:c.1597T>A
NM_000329.3(RPE65):c.1597T>A (p.Ser533Thr)
NC_000001.11:g.68429781A>T
CM000663.2:g.68429781A>T
NC_000001.10:g.68895464A>T
CM000663.1:g.68895464A>T
NC_000001.9:g.68668052A>T
NG_008472.1:g.25179T>A
NG_008472.2:g.25179T>A
ENST00000262340.6:c.1597T>A
ENST00000262340.5:c.1597T>A
NM_000329.2:c.1597T>A

Uncertain Significance

Met criteria codes 1

PM2_Supporting

Not Met criteria codes 3

PP3 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:c.1597T>A is a missense variant in RPE65 causing substitution of serine with threonine at position 533. This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.00002596, with 3 alleles / 30608 total alleles in the South Asian 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 0.568, which is below the ClinGen LCA / eoRD VCEP threshold of ≥ 0.644 and does not predict a damaging effect on RPE65 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.00 for all change types, which is below the ClinGen

LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. At least one proband harboring this variant exhibits a phenotype including a diagnosis of Leber congenital amaurosis, however other available phenotypes are not sufficient to evaluate specificity for RPE65-related recessive retinopathy and no second variant has been identified, so PP4 is not met (PMID: 17964524). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state (PMID: 25097241). However, the proband was not counted for PM3_Supporting because the NM_000329.3(RPE65):c.89T>C (p.Val30Ala) variant suspected in trans has not yet been classified for RPE65-related recessive retinopathy and because sufficient phenotype information was not available. In summary, this variant meets the criteria to be classified as a variant of uncertain significance for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: PM2_Supporting (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM2_Supporting	✔	This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.00002596, with 3 alleles / 30608 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

PP3	✖	The computational predictor REVEL gives a score of 0.568, which is below the ClinGen LCA / eoRD VCEP threshold of ≥ 0.644 and does not predict a damaging effect on RPE65 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.00 for all change types, 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 consistent with retinitis pigmentosa, but details are not sufficiently reported to consider specificity for RPE65-related recessive retinopathy, so PP4 is not met (PMID: 25097241).
PM3	✖	At least one proband harboring this variant is compound heterozygous for the p.Val30Ala variant (without confirmation in trans) and exhibits a phenotype consistent with retinitis pigmentosa, but details are not sufficiently reported to consider inclusion in PM3 (PMID: 25097241). The p.Val30Ala variant is rare but has not yet been submitted to ClinVar or classified by the ClinGen Leber congenital amaurosis / early onset retinal dystrophy VCEP.

Curation History

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