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Variant: NM_000329.3(RPE65):c.881A>C (p.Lys294Thr)

Version: 1.0

CA146043

92859 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 745e5fa1-6a0a-4022-b6e4-db8bbc8fb126
Approved on: 2024-02-20
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HGVS expressions

NM_000329.3:c.881A>C
NM_000329.3(RPE65):c.881A>C (p.Lys294Thr)
NC_000001.11:g.68439059T>G
CM000663.2:g.68439059T>G
NC_000001.10:g.68904742T>G
CM000663.1:g.68904742T>G
NC_000001.9:g.68677330T>G
NG_008472.1:g.15901A>C
NG_008472.2:g.15901A>C
ENST00000262340.6:c.881A>C
ENST00000262340.5:c.881A>C
NM_000329.2:c.881A>C

Likely Benign

Met criteria codes 2

PP3_Moderate BA1

Not Met criteria codes 8

BS4 BS3 BP4 BP2 PS3 PP4 PM3 PM5

Evidence Links 1

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.881A>C is a missense variant that causes substitution of lysine with threonine at position 294. This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.03554, with 1312 alleles / 35390 total alleles in the Admixed American population (with 33 homozygotes), which is higher than the ClinGen LCA / eoRD VCEP BA1 threshold of >0.008 (BA1). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who harbored the variant in the heterozygous state (PMID: 19431183) with the NM_000329.3(RPE65):c.1078G>C (p.Ala360Pro) variant in trans and a 22-bp deletion within exon 12 in cis (PMID:

19431183). However, the proband was not counted for the PM3 or BP2 codes because the other two variants have not yet been classified by the ClinGen LCA / eoRD VCEP. The meta-predictor REVEL gives a score of 0.974, which is above the ClinGen LCA/eoRP VCEP PP3 threshold of >0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The variant exhibited 16%-68% enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is between the ClinGen LCA / eoRD VCEP thresholds of <10% activity (PS3_Supporting) and >50% activity (BS3_Supporting), so neither functional study code is met (PMID: 16150724, PMID: 19431183). Another missense variant in the same codon, NM_000329.2; c.880A>G, (p.Lys294Glu), has been observed in a proband with early-onset severe retinal dystrophy (VCEP member-provided data), but has been classified as a variant of uncertain significance for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP, so the PM5_Supporting code is not met. In summary, this variant meets the criteria to be classified as likely benign for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: BA1 and PP3_Moderate. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP3_Moderate	✔	The meta-predictor REVEL gives a score of 0.974, which is above the ClinGen LCA/eoRP VCEP PP3 threshold of >0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
BA1	✔	This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.03554, with 1312 alleles / 35390 total alleles in the Admixed American population (with 33 homozygotes), which is higher than the ClinGen LCA / eoRD VCEP BA1 threshold of >0.008 (BA1).

Not Met criteria codes

BS4	✖	This variant has been reported not to segregate with Leber congenital amaurosis in an affected family member (PMID: 11095629). However, the other affected family member also harbors the variant in a heterozygous state, indicating inconsistency with the cause of disease in either sibling.
BS3	✖	Isomerohydrolase activity assay in 293-derived cells expressing recombinant RPE65 showed either 16% (PMID: 16150724) or 68% (PMID: 19431183) of wild-type enzymatic activity, indicating that this variant has a hypomorphic, slightly damaging effect on protein function, so that BS3 is not met. Isomerohydrolase activity assay in 293T-LC cells expressing exogenous Rpe65 from the pRK5 vector showed only 68% of wild-type enzymatic activity, indicating that this variant has a damaging effect on protein function (Table 2). PubMed:19431183
BP4	✖	The meta-predictor REVEL gives a score of 0.974, which is above the ClinGen LCA/eoRP VCEP BP4 threshold of <0.3, while SpliceAI does not identify a suspected splicing defect. The computational evidence fails to meet this criterion.
BP2	✖	The variant was observed in the heterozygous state in a family harboring two other variations in the RPE65 gene: p.Ala360Pro (in trans, ClinVar: 98823) and a 22-bp deletion in exon 12 (in cis, not identified in sufficient detail to determine correct nomenclature) predicted to excise codons 427 to 434 in the mature protein (PMID: 19431183). These other variants may be pathogenic but have not yet been evaluated by the VCEP specifications. This criterion has not yet been met.
PS3	✖	Isomerohydrolase activity assay in 293-derived cells expressing recombinant RPE65 showed either 16% (PMID: 16150724) or 68% (PMID: 19431183) of wild-type enzymatic activity, indicating that this variant has a hypomorphic, slightly damaging effect on protein function, so that PS3_supporting is not met.

Isomerohydrolase activity assay in 293T-LC cells expressing exogenous Rpe65 from the pRK5 vector showed only 68% of wild-type enzymatic activity, indicating that this variant has a damaging effect on protein function (Table 2).
PubMed:19431183

PP4		✖	In one study, the three affected probands harbored the variant in the heterozygous state with no identified second variant in RPE65, and without genotyping of other loci associated with inherited retinal disease (PMID: 11095629). In a second study, four probands harbored the variant in the heterozygous state with no identified second variant in RPE65, while an additional proband harbored the variant with another RPE65 variant in cis and a third RPE65 variant in trans (PMID: 19431183). Because the presence of two RPE65 variants are required for consideration for this code, PP4 is not met.
PM3		✖	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who harbored the variant in the heterozygous state (PMID: 19431183) with the NM_000329.3(RPE65):c.1078G>C (p.Ala360Pro) variant in trans and a 22-bp deletion within exon 12 in cis (PMID: 19431183). However, the proband was not counted for the PM3 or BP2 codes because the other variants have not yet been classified by the ClinGen LCA / eoRD VCEP.
PM5		✖	Another missense variant in the same codon, NM_000329.2; c.880A>G, (p.Lys294Glu), has been observed in a proband with early-onset severe retinal dystrophy (VCEP member-provided data), but has been classified as a variant of uncertain significance for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP, so the PM5_Supporting code is not met.

Curation History

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