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.302C>T (p.Thr101Ile)

Version: 1.0

CA340748300

865946 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: e886266e-2f44-4bb3-96a0-eb3bfb13599b
Approved on: 2024-12-12
Published on: 2024-12-12

HGVS expressions

NM_000329.3:c.302C>T
NM_000329.3(RPE65):c.302C>T (p.Thr101Ile)
NC_000001.11:g.68444827G>A
CM000663.2:g.68444827G>A
NC_000001.10:g.68910510G>A
CM000663.1:g.68910510G>A
NC_000001.9:g.68683098G>A
NG_008472.1:g.10133C>T
NG_008472.2:g.10133C>T
ENST00000262340.6:c.302C>T
ENST00000262340.5:c.302C>T
NM_000329.2:c.302C>T

Likely Pathogenic

Met criteria codes 4

PS3_Supporting PM3 PM2_Supporting PP3_Moderate

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

The NM_000329.3(RPE65):c.302C>T (p.Thr101Ile) variant is a missense variant in RPE65 causing a substitution of threonine with isoleucine at position 101. This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 8.474e-7, with 1 / 1180026 alleles in the European (Non-Finnish) 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 0.88, which is above the ClinGen LCA/eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The variant exhibited 1.27% enzymatic activity in a retinoid

isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA/eoRD PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, PMID: 19431183). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.271C>T p.Arg91Trp variant confirmed in trans by next-generation sequencing data (1 point, VCEP member-provided data), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PM3). 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, PP3_Moderate, PS3_Supporting, PM3 (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PS3_Supporting ✔	The variant exhibited 1.27% enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, PMID: 19431183).
PM3 ✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.271C>T p.Arg91Trp variant confirmed in trans by next-generation sequencing data (1 point, VCEP member-provided data), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PM3).
PM2_Supporting ✔	This variant is present in gnomAD v.4.1.0 at a Grpmax allele frequency of 8.474e-7, with 1 / 1180026 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_Moderate ✔	The computational predictor REVEL gives a score of 0.88, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Curation History

Showing 1 to 2 of 2 rows