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Variant: NM_000329.3(RPE65):c.1583G>T (p.Gly528Val)

Version: 1.0

CA340740566

801494 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6ebf5afc-0dc3-41a6-9a87-da2942d5315d
Approved on: 2025/6/11
Published on: 2025/6/11

HGVS expressions

NM_000329.3:c.1583G>T
NM_000329.3(RPE65):c.1583G>T (p.Gly528Val)
NC_000001.11:g.68429795C>A
CM000663.2:g.68429795C>A
NC_000001.10:g.68895478C>A
CM000663.1:g.68895478C>A
NC_000001.9:g.68668066C>A
NG_008472.1:g.25165G>T
NG_008472.2:g.25165G>T
ENST00000262340.6:c.1583G>T
ENST00000262340.5:c.1583G>T
NM_000329.2:c.1583G>T

Likely Pathogenic

Met criteria codes 5

PS3_Supporting PM2_Supporting PM3 PP4 PP3_Moderate

Not Met criteria codes 2

BA1 PP2

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.1583G>T (p.Gly528Val) is a missense variant that replaces glycine with valine at amino acid 528. This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.0000008477, with 1 allele / 1,179,706 total alleles in the European (non-Finnish) 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 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.669delCA (now known as NM_000329.3(RPE65):c.615_616del (p.Ile206fs)) variant suspected in trans (0.5 points, PMID: 11095629), which was

previously classified pathogenic by the ClinGen LCA / eoRD VCEP. This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.11+5G>A variant suspected in trans (0.5 points, PMID: 32865313), which was 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), night blindness (0.5 pts), nystagmus, (1 pt), poor central visual acuity (1 pt), visual field constriction (1 pt), and nonrecordable electroretinogram responses (0.5 pts for rods and 1 for cones), which together are specific for RPE65-related recessive retinopathytotal 5.5 points, PMID: 11095629, PP4). The computational predictor REVEL gives a score of 0.982, 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 <2 % enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD VCEP PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, PMID: 16150724). 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, PP4, PP3_Moderate, and PS3_Supporting. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PS3_Supporting	✔	The variant exhibited <2 % enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD VCEP PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, PMID: 16150724).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 8.477e-7, with 1 allele / 1179706 total alleles in the European (non-Finish) population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.669delCA (now known as c.615_616del) variant suspected in trans (0.5 points, PMIDs: 11095629), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP.This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.11+5G>A variant suspected in trans (0.5 points, PMIDs: 32865313), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP. (1 total point, PM3).
PP4	✔	At least one proband (LCA816) harboring this variant exhibits a phenotype including Leber congenital amaurosis diagnosis (0.5 pt), night blindness (0.5 pt), nystagmus, (1.0 pt), poor central visual acuity (1.0 pt), visual field constriction (1.0 pt), and nonrecordable ERG responses (0.5 pt for rods and 1.0 for cones LCA816), which together are specific for RPE65-related recessive retinopathytotal 5.5 points, PMID: 11095629, PP4).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.982, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	112/343 (32.7%) of the pathogenic/likely pathogenic variants on ClinVar are missense which is below the threshold of 0.8. gnomAD missesense z score of 0.29, which is below +1.96 (95%).

Curation History

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