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Variant: NM_000329.3(RPE65):c.1451G>T (p.Gly484Val)

Version: 1.0

CA902151

813222 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 28d19f3d-84d3-41a4-961e-ce9e607a350c
Approved on: 2024/4/22
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HGVS expressions

NM_000329.3(RPE65):c.1451G>T (p.Gly484Val)
NM_000329.3:c.1451G>T
NC_000001.11:g.68429927C>A
CM000663.2:g.68429927C>A
NC_000001.10:g.68895610C>A
CM000663.1:g.68895610C>A
NC_000001.9:g.68668198C>A
NG_008472.1:g.25033G>T
NG_008472.2:g.25033G>T
ENST00000262340.6:c.1451G>T
ENST00000262340.5:c.1451G>T
NM_000329.2:c.1451G>T

Pathogenic

Met criteria codes 6

PP3_Moderate | PP4 | PS1_Moderate | PM3_Strong | PM2_Supporting | PP1_Moderate

Not Met criteria codes 1

PM5

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.1451G>T (p.Gly484Val) is a putative missense variant located in the first nucleotide of exon 14 that is predicted to cause the replacement of glycine with valine at codon 484. The computational predictor REVEL gives a score of 0.991, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.56, which is above the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing (PP3_Moderate). Another missense variant at the same nucleotide, NM_000329.3(RPE65):c.1451G>A (p.Gly484Asp), has been

classified as likely pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP and has a SpliceAI score of 0.23 for acceptor loss, indicating that both variants are predicted to have a damaging impact on splicing (PMID: 30025081, PMID: 34492281, PS1_Moderate). This variant is present in gnomAD v2.1.1 at a GrpMax allele frequency of 0.000002990, with 2 alleles / 111,040 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 3 unrelated probands with early-onset severe retinal dystrophy who are homozygous for the variant (1 pt, PMID: 33308271, PMID: 32531858, PMID: 33472769). The 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.272G>A (p.Arg91Gln) variant confirmed in trans (1 pt, PMID: 38002999), which was previously classified pathogenic or likely pathogenic by the ClinGen LCA / eoRD VCEP (2 total pts, PM3_Strong). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PMID: 33308271, PP1_Moderate). At least one proband harboring this variant exhibits a phenotype including clinical diagnosis of Leber congenital amaurosis (0.5 pts), symptomatic onset at age 3 months (1 pt), extinguished ERG responses from rods (0.5 pts) and cones, optic nerve pallor (0.5 pts), macular atrophy (0.5 pts), decreased peripheral vision (1 pt), abnormal color vision (1 pt), decreased central visual acuity (1 pt), nystagmus (1 pt), which together are specific for RPE65-related recessive retinopathy (total 7 pts, PMID: 33308271, PP4). In summary, this variant meets the criteria to be classified as pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: PS1_moderate, PM2_supporting, PM3_strong, PP1_moderate, PP3, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.991, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function. Additionally, the splicing impact predictor, SpliceAI, gives a score of 0.56, which is above the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing (PP3_Moderate).
PP4	✔	At least one proband (6-52) harboring this variant exhibits a phenotype including an extinguished ERG and clinical diagnosis of LCA (0.5 points), optic nerve pallor (0.5 points), macular atrophy (0.5), symptomatic onset at 3 months (1), decreased peripheral vision (1), abnormal color vision (1), decreased central visual acuity (1), nystagmus (1), which together are specific for RPE65-related recessive retinopathy (6.5 points, PMID: 33308271, PP4).
PS1_Moderate	✔	Another missense variant at the same nucleotide (NM_000329.3(RPE65):c.1451G>A (p.Gly484Asp)) has been classified likely pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP and has a SpliceAI score of 0.23 for acceptor loss (PMID: 30025081, PMID: 34492281).
PM3_Strong	✔	This variant has been reported in at least 3 unrelated probands with early-onset severe retinal dystrophy who are homozygous for the variant (1 point, PMIDs: 33308271, 32531858, 33472769). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who is compound heterozygous with the RPE65:c.272G>A, pArg91Asn variant confirmed in trans and classified as pathogenic by the ClinGen LCA/eoRD VCEP (1 point, PMID: 38002999). (2 total points, PM3_Strong).
PM2_Supporting	✔	This variant is present in gnomAD v2.1.1 at a Grp Max allele frequency of 0.000002990, with 2 alleles / 111,040 total alleles in the European (Non-Finnish) population, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0002(PM2).
PP1_Moderate	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PMID: 33308271)(PP1_Moderate).

Not Met criteria codes

PM5 ✖

Another missense variant in the same codon (NM_000329.3(RPE65):c.1451G>A (p.Gly484Asp)) has been classified likely pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PMID: 30025081, PMID: 34492281). Splicing prediction using SpliceAI predicted an effect on splicing for both of these variants, with scores of 0.56 and 0.23 respectively for acceptor loss. Because these scores are not within 10% of each other, PM5 is not met.

Curation History

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