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Variant: NM_000329.3(RPE65):c.1440AGA[1] (p.Glu481del)

Version: 1.0

CA523749345

973961 (ClinVar)

Gene: RPE65
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: ae504942-bc6d-4d65-b6d7-87e2b89ef68a
Approved on: 2025/6/11
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HGVS expressions

NM_000329.3(RPE65):c.1440AGA[1] (p.Glu481del)
NM_000329.3:c.1440AGA[1]
NC_000001.11:g.68431075_68431077del
CM000663.2:g.68431075_68431077del
NC_000001.10:g.68896758_68896760del
CM000663.1:g.68896758_68896760del
NC_000001.9:g.68669346_68669348del
NG_008472.1:g.23888_23890del
NG_008472.2:g.23888_23890del
ENST00000262340.6:c.1443_1445del
ENST00000262340.5:c.1443_1445del
NM_000329.2:c.1443_1445del
NM_000329.3:c.1443_1445del

Likely Pathogenic

Met criteria codes 4

PM3 PM4_Supporting PP4_Moderate PM2_Supporting

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.1443_1445del (p.Glu481del) is an in-frame deletion encoding 1 amino acid in a non-repeat region, predicted to cause a change in the length of the protein, with at least one of the deleted base pairs highly conserved with a PhyloP conservation score of 7.5 (PM4_Supporting). The variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.00002287, with 35 alleles / 1,179,000 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 homozygous for the variant (0.5 points, VCEP member-provided data). This variant has also been reported in at least 2 apparently unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.989G>A (p.Cys330Tyr) variant suspected but not confirmed in trans, which has been previously classified as likely pathogenic by the ClinGen LCA/eoRD VCEP (0.25 points), or the NM_000329.3(RPE65):c.370C>T (p.Arg124Ter) variant suspected but not confirmed in trans, which has been previously classified as pathogenic by the ClinGen LCA/eoRD VCEP (0.5 points). This variant has been reported in at least 1 proband with retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.11+5G>A variant suspected but not confirmed in trans, which has been previously classified as pathogenic by the ClinGen LCA/eoRD VCEP, however, this final proband did not have available phenotype details to confirm the exact diagnosis and could not be included in PM3 (1.25 total points, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), absent or severely reduced electroretinogram responses (0.5 pts), congenital night blindness (0.5 pts), pigmentary retinopathy with attenuated vessels (0.5 pts), poor pupillary light response (0.5 pts), retinal pigment epithelium mottling (0.5 pts), macular atrophy (0.5 pts), symptomatic onset between birth and age 5 years (1 pt), optical coherence tomography preserved with respect to vision loss (1 pt), decreased peripheral vision (1 pt), abnormal color vision or evidence of cone involvement on electroretinogram (1 pt), decreased central visual acuity (1 pt), nystagmus (1 pt), absence or minimal autofluorescence (2 pts), previous exome / genome / 100+ not providing an alternative explanation for disease (2 pts), and participation in a gene therapy trial with strict inclusion criteria and documented improvement of full-field stimulus threshold response after RPE65 gene therapy, including subjectively improved vision in dim light (2 pts), which together are highly specific for RPE65-related recessive retinopathy (15.5 total points, VCEP member-provided data, PP4_Moderate). 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, PM4_Supporting, and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, VCEP member-provided data). This variant has also been reported in at least 2 apparently unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.989G>A (p.Cys330Tyr) variant suspected but not confirmed in trans, which has been previously classified as likely pathogenic by the ClinGen LCA/eoRD VCEP (0.25 points), or the NM_000329.3(RPE65):c.370C>T (p.Arg124Ter) variant suspected but not confirmed in trans, which has been previously classified as pathogenic by the ClinGen LCA/eoRD VCEP (0.5 points). This variant has been reported in at least 1 proband with retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.11+5G>A variant suspected but not confirmed in trans, which has been previously classified as pathogenic by the ClinGen LCA/eoRD VCEP, however, this final proband did not have available phenotype details to confirm the diagnosis and could not be included in PM3 (1.25 total points, PM3).
PM4_Supporting	✔	This variant is predicted to cause a change in the length of the protein due to an in-frame deletion encoding 1 amino acids in a non-repeat region, with at least one of the deleted base pairs highly conserved with a PhyloP conservation score of 7.5 (PM4_Supporting).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts), absent or severely reduced ERG responses (0.5 pts), congenital night blindness (0.5 pts), pigmentary retinopathy with attenuated vessels (0.5 pts), poor pupillary light response (0.5 pts), RPE mottling (0.5 pts), macular atrophy (0.5 pts), symptomatic onset between birth and age 5 years (1 pt), OCT preserved with respect to vision loss (1 pt), decreased peripheral vision (1 pt), abnormal color vision or evidence of cone involvement on ERG (1 pt), decreased central visual acuity (1 pt), nystagmus (1 pt), absence or minimal autofluorescence (2 pts), previous exome / genome / 100+ not providing an alternative explanation (2 pts), and participation in a gene therapy trial with strict inclusion criteria and documented great FST response after RPE65 gene therapy, including subjectively improved vision in dim light (2 pts), which together are specific for RPE65-related recessive retinopathy to meet the PP4 code (15.5 total points, VCEP member-provided data).

PM2_Supporting		✔	This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00002287, with 35 alleles / 1179000 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).

Curation History

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