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Variant: NM_000329.3(RPE65):c.11+5G>A

Version: 1.0

CA226483

98825 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: e3150cbe-1294-43a0-bd9e-f945d8394fdb
Approved on: 2023-12-22
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HGVS expressions

NM_000329.3:c.11+5G>A
NM_000329.3(RPE65):c.11+5G>A
NC_000001.11:g.68449890C>T
CM000663.2:g.68449890C>T
NC_000001.10:g.68915573C>T
CM000663.1:g.68915573C>T
NC_000001.9:g.68688161C>T
NG_008472.1:g.5070G>A
NG_008472.2:g.5070G>A
ENST00000262340.6:c.11+5G>A
ENST00000262340.5:c.11+5G>A
NM_000329.2:c.11+5G>A

Pathogenic

Met criteria codes 6

PP1 PP3 PM2_Supporting PS3_Supporting PP4_Moderate PM3_Very Strong

Not Met criteria codes 2

BA1 BS1

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.11+5G>A variant is a putative splicing variant in intron 1 of the RPE65 gene. The computational splicing predictor SpliceAI lists a change score of 0.58 for splice donor gain, predicting a deleterious impact on splicing (PP3). VCEP-member provided data from a mini-gene assay in HEK-293 cells show that this variant reduces normal splicing and leads to >400x reduction of mature mRNA, relative to the wild-type control (PS3_Supporting, Guan et al., 2024). At least 3 patients with this variant have been reported with detailed phenotypes (PMID: 21211845, PMID: 11786058), one of whom exhibited nonrecordable ERG responses from rods

(0.5 pts) and cones (1 pt), congenital night blindness (0.5 pts), absence of autofluorescence (2 pts), optic nerve pallor (0.5 pts), RPE granularity (0.5 pts), onset between birth and age 5 years (1 pt), OCT preserved at macula (1 pt), constricted Goldmann visual field (1 pt), decreased central visual acuity (1 pt), and nystagmus (1 pt), which together are highly specific for recessive RPE65 retinopathy (10 pts total, VCEP member-provided data, PP4_Moderate). This variant has been detected in at least 7 published cases with recessive retinopathy, including at least two individuals homozygous for the variant (1 pt) and three individuals compound heterozygous for this variant in trans with either the c.615_616del (p.Ile206Cysfs*27), p.Glu102Ter, or c.89dup (p.Thr31fs) variant, all which have been classified Pathogenic by this VCEP (4pts, PMID: 11095629, PMID: 17525851, PMID: 35129589), (PM3_Very-Strong). Two publications contain segregation data (PMID: 11786058 and PMID: 35001204), with one set of genotype-positive siblings exhibiting the required phenotype of absent or severely decreased rod electroretinogram response (PP1). The GrpMax Filtering AF for this variant in gnomAD v2.1.1 is 0.0001017 (PM2_Supporting). 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: PM3_Very-Strong, PP4_Moderate, PP1, PM2_Supporting, PP3, PS3_Supporting. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP1	✔	Two publications contain segregation data (PMID: 11786058 and PMID: 35001204), although only one specifies that the two siblings each exhibited the required phenotype of absent or severely decreased rod electroretinogram response (PMID: 11786058, PP1).
PP3	✔	The computational splicing predictor SpliceAI lists a change score of 0.58 for splice donor gain, predicting a deleterious impact on splicing (PP3).
PM2_Supporting	✔	The Popmax Filtering AF for this variant in gnomAD v2.1.1 is 0.0001017, which is lower than the ClinGen LCA/eoRP VCEP threshold (<0.0002) (PM2_Supporting).
PS3_Supporting	✔	VCEP-member provided data from a mini-gene assay in HEK-293 cells show that this variant reduces normal splicing and leads to >400x reduction of mature mRNA, relative to the wild-type control (PS3_Supporting).
PP4_Moderate	✔	A proband with this variant (VCEP-provided data) exhibited nonrecordable ERG and congenital night blindness (required), absence of autofluorescence / only hyperfluorescence at the macula (specific, 2 points), optic nerve pallor (0.5 points), RPE granularity/mottling (0.5 points), onset between birth and age 5 years (1 point), OCT preserved at macula (1 point), decreased peripheral vision / constricted GVF (1 point), evidence of cone involvement on ERG (nonrecordable, 1 point), decreased central visual acuity (1 point), nystagmus (reported by family before age 8 months, 1 point), which together was highly specific for recessive RPE65 retinopathy (9 points, PP4_Moderate). A second patient with this variant (PMID: 21211845) displayed nonrecordable ERG and night blindness, as well as other phenotypes that scored 5 points total. These included Fundus albipunctatus (2 points), Hypoautofluorescence (2 points), and decreased central vision acuity (1 point). A third proband with this variant (PMID: 11786058) displayed nonrecordable ERG and congenital nyctalopia, as well as other phenotypes that scored a total of 5.5 points, including Pigmentary retinopathy with attenuated vessels (0.5), Symptomatic onset between birth and age five years (1), Decreased peripheral vision (1), Abnormal color vision or evidence of cone involvement on ERG (1), Decreased central visual acuity (1), and Nystagmus (1). 6 additional probands who do not meet PP4 are reported in PMID: 20683928, 2 more in PMID: 25257057, 2 more in PMID: 9326941, 1 more in PMID: 12960219, and 3 more in PMID: 19854499.
PM3_Very Strong	✔	This variant has been detected in at least 7 individuals with recessive retinopathy. At least 2 individuals homozygous for the variant have met the minimum phenotype requirement of absent or severely reduced rod ERG responses (PMID: 9326941, PMID: 11095629, 1pt). At least three individuals are compound heterozygous for this variant with segregation analysis confirming its presence in trans with either c.615_616del (p.Ile206Cysfs*27), p.Glu102Ter, or c.89dup (p.Thr31fs), all classified Pathogenic by this VCEP (3pt, PMID: 11095629, PMID: 17525851). Another

compound heterozygous proband harbors this variant and p.Arg234Ter, but does not have confirmation that they are in trans (0.5pt), (PM3_Very_Strong). 3 individuals were compound heterozygous for the variant in trans with a variant that has not yet been classified by the VCEP (NM_000329.3(RPE65):c.858+1G>T, NM_000329.3(RPE65):c.1102T>C (p.Tyr368His), NM_000329.3(RPE65):c.344T>C (p.Ile115Thr), PMID: 9326941, PMID: 11786058, PMID: 21211845, ClinVar Variation IDs: 98893, 29870, 1066633). These probands were not considered for this criterion to avoid circularity. An additional proband from VCEP member-provided data was compound heterozygous for this variant in trans with the c.1249G>C (p. Glu417Gln) variant, but was not considered to avoid circularity.

Not Met criteria codes

BA1	✖	The Popmax Filtering AF for this variant in gnomAD v2.1.1 is 0.0001017, which is lower than the ClinGen LCA/eoRP VCEP threshold (>0.00816) for this criterion.
BS1	✖	The Popmax Filtering AF for this variant in gnomAD v2.1.1 is 0.0001017, which is lower than the ClinGen LCA/eoRP VCEP threshold (>0.000816) for this criterion.

Curation History

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