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Variant: NM_000329.3(RPE65):c.1101A>G (p.Arg367=)

Version: 1.1

CA418279061

427868 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 120fa1fa-db34-4def-8b2e-7c52451328b2
Approved on: 2026/8/20
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HGVS expressions

NM_000329.3(RPE65):c.1101A>G (p.Arg367=)
NM_000329.3:c.1101A>G
NC_000001.11:g.68438214T>C
CM000663.2:g.68438214T>C
NC_000001.10:g.68903897T>C
CM000663.1:g.68903897T>C
NC_000001.9:g.68676485T>C
NG_008472.1:g.16746A>G
NG_008472.2:g.16746A>G
ENST00000262340.6:c.1101A>G
ENST00000262340.5:c.1101A>G
NM_000329.2:c.1101A>G

Pathogenic

Met criteria codes 4

PVS1 | PM2_Supporting | PM3 | PP4

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*
- **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.1101A>G (p.Arg367=) is a synonymous variant located in the third nucleotide of exon 10. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The splicing impact predictor SpliceAI gives a score of 0.99 for donor gain, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing. This prediction has been confirmed by a minigene assay showing complete disruption of splicing and production of an alternative transcript with an out-of-frame truncation of 28 base pairs, which is supportive of a damaging effect on protein function (PMID: 28714225). These in silico and experimental findings

have not been used to meet the PP3 and PS3_Supporting codes, but rather combined to meet the PVS1(RNA) code. At least one proband harboring this variant exhibits a phenotype including clinical diagnosis of Leber congenital amaurosis (0.5 pts), previous 100+ retinal dystrophy gene panel testing that did not provide an alternative explanation for visual impairment (2 pts), decreased central visual acuity (1 pt), onset between birth and 5 years old (1 pt), pigmentary retinopathy with attenuated vessels (0.5 pts), RPE mottling (0.5 pts) and macular atrophy (0.5 pts), which together are specific for RPE65-related recessive retinopathy (6 pts, PMID: 28714225, PMID: 32865313, PP4). This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.1022T>C (p.Leu341Ser) or NM_000329.3(RPE65):c.272G>A (p.Arg91Gln) variants suspected in trans (1 point, PMID: 36909829, 28714225), which were previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (PM3). 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: PVS1, PM2_Supporting, PM3, PP4. (VCEP specifications version 1.0.0).

Met criteria codes

PVS1	✔	A well-established in vitro functional study with RNA splicing data (PMID: 28714225) is supportive of a damaging effect with evidence of alternative transcript production at complete levels, relative to normal allele. The variant-containing transcript shows an out-of-frame 28 base pair truncation corresponding to the use of the variant-created novel splice site (PVS1). This is consistent with the splicing impact predictor SpliceAI giving a score of 0.99 for splice donor gain.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (PM2_Supporting).
PM3	✔	This variant has been reported in at least 2 proband(s) with early-onset severe retinal dystrophy who were compound heterozygous with either the Leu341Ser or Arg91Gln variants suspected in trans (1 point, PMID: 36909829, 28714225), which were previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (PM3).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including clinical diagnosis of Leber congenital amaurosis (0.5 pt), previous 100+ retinal dystrophy gene panel testing that did not provide an alternative explanation for visual impairment (2 pt), decreased central visual acuity (1 pt), onset between birth and 5 years old (1 pt), pigmentary retinopathy with attenuated vessels (0.5 pt), RPE mottling (0.5 pt) and macular atrophy (0.5), which together are specific for RPE65-related recessive retinopathy (6 points, PMID: 28714225, 32865313; PP4).

Curation History

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