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Variant: NM_000329.3(RPE65):c.1338+1G>A

Version: 1.0

CA16043370

374139 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2996ff38-ed57-4997-83c7-626230be956e
Approved on: 2025-03-27
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HGVS expressions

NM_000329.3:c.1338+1G>A
NM_000329.3(RPE65):c.1338+1G>A
NC_000001.11:g.68431281C>T
CM000663.2:g.68431281C>T
NC_000001.10:g.68896964C>T
CM000663.1:g.68896964C>T
NC_000001.9:g.68669552C>T
NG_008472.1:g.23679G>A
NG_008472.2:g.23679G>A
ENST00000262340.6:c.1338+1G>A
ENST00000262340.5:c.1338+1G>A
NM_000329.2:c.1338+1G>A

Pathogenic

Met criteria codes 5

PM3_Supporting PM2_Supporting PVS1 PP1 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 1.0.0*
- **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.1338+1G>A variant disrupts a canonical splice site in intron 12 and is predicted to lead to skipping of a critical exon, resulting in a frameshift, and likely nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1). This variant has been reported in 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.1207_1210dup (p.Glu404AlafsTer4) variant confirmed in trans (0.5 points, PMID 32367544), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (0.5 total points, PM3_Supporting).The variant has been reported to

segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 32367544). At least one proband harboring this variant was tested by exome sequencing (2.0) and exhibits a phenotype including optic disc pallor (0.5), pigmentary retinopathy with attenuated vessels (0.5), poor pupillary light response (0.5), RPE mottling (0.5), macular atrophy (0.5), and decreased peripheral (1.0) and central vision (1.0) which together are specific for RPE65-related recessive retinopathy (6.5 points, PMID: 32367544, PP4). This variant is present in gnomAD v.4.1.0 at an allele frequency of 8.478e-7 with 1/1179592 total alleles in the European (non-Finnish) population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002. 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, PP1, PP4, PM3_supporting. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3_Supporting	✔	This variant has also been reported in 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.1207_1210dup (p.Glu404AlafsTer4) variant confirmed in trans (0.5 points, PMID 32367544), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (0.5 total points, PM3_Supporting).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at an allele frequency of 8.478e-7, 1 alleles / 1179592 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)
PVS1	✔	This variant disrupts a canonical splice site in intron 12 and is predicted to lead to skipping of a critical exon, resulting in a frameshift, and likely nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1).
PP1	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 32367544).
PP4	✔	At least one proband harboring this variant was tested by exome sequencing (2.0) and exhibits a phenotype including optic disc pallor (0.5), pigmentary retinopathy with attenuated vessels (0.5), poor pupillary light response (0.5), RPE mottling (0.5), macular atrophy (0.5), and decreased peripheral (1.0) and central vision (1.0) which together are specific for RPE65-related recessive retinopathy (6.5) points, PMID: 32367544, PP4).

Curation History

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