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Variant: NM_000329.3(RPE65):c.444_445del (p.Glu148fs)

Version: 1.0

CA1173563400

973966 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2a23c55c-4afc-4e98-96e0-8ef8e09266e7
Approved on: 2025/6/30
Published on: 2025/6/30

HGVS expressions

NM_000329.3:c.444_445del
NM_000329.3(RPE65):c.444_445del (p.Glu148fs)
NC_000001.11:g.68444584_68444585del
CM000663.2:g.68444584_68444585del
NC_000001.10:g.68910267_68910268del
CM000663.1:g.68910267_68910268del
NC_000001.9:g.68682855_68682856del
NG_008472.1:g.10378_10379del
NG_008472.2:g.10378_10379del
ENST00000262340.6:c.444_445del
ENST00000262340.5:c.444_445del
NM_000329.2:c.444_445del

Pathogenic

Met criteria codes 3

PM3 PM2_Supporting PVS1

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.444_445del (p.Glu148AspfsTer8) is a frameshift variant that introduces a premature stop codon into exon 5 of 14, and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.1102T>C (p.Tyr368His) variant confirmed in trans, which was previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (1 point, VCEP member-provided data, 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, and PM3. (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 compound heterozygous with the NM_000329.3(RPE65):c.1102T>C (p.Tyr368His) variant confirmed in trans, which was previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (1 point, VCEP member-provided data, PM3).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1	✔	This is a frameshift variant that introduces a premature stop codon into exon 5 of 14, and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1).

Curation History

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