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Variant: NM_000329.3:c.825C>A

Version: 1.0

CA340745588

3024120 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 712bf686-0d03-4824-828c-16e06bf93992
Approved on: 2024-02-20
Published on: 2024-02-20

HGVS expressions

NM_000329.3:c.825C>A
NC_000001.11:g.68439224G>T
CM000663.2:g.68439224G>T
NC_000001.10:g.68904907G>T
CM000663.1:g.68904907G>T
NC_000001.9:g.68677495G>T
NG_008472.1:g.15736C>A
NG_008472.2:g.15736C>A
ENST00000262340.6:c.825C>A
ENST00000262340.5:c.825C>A
NM_000329.2:c.825C>A

Pathogenic

Met criteria codes 3

PP4 PVS1 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

The NM_000329.3(RPE65):c.825C>A (p.Tyr275Ter) variant is a nonsense variant that introduces a premature stop codon into exon 8 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 v2.1.1 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including congenital night blindness (0.5 pts), extinguished rod ERG responses (0.5 pts), previous exome sequencing that did not provide an alternative explanation for visual impairment (2 pts), symptomatic onset between birth and age five years (1 pt), retinal degeneration with attenuated vessels (0.5 pts), and extinguished cone ERG responses (1 pt), which together are specific for RPE65-related recessive

retinopathy (5.5 points, PMID: 31273949, PP4). 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, PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP4	✔	At least one proband harboring this variant exhibits a phenotype including congenital night blindness (0.5 pt), extinguished rod ERG responses (0.5 pt), previous exome sequencing that did not provide an alternative explanation for visual impairment (2 pt), symptomatic onset between birth and age five years (1 pt), retinal degeneration with attenuated vessels (0.5 pt), and extinguished cone ERG responses (1 pt), which together are specific for RPE65-related recessive retinopathy (5.5 points, PMID: 31273949, PP4).
PVS1	✔	This is a nonsense variant that introduces a premature stop codon into exon 8 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).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Curation History

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