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Variant: NM_000329.3:c.16G>T

Version: 1.0

CA340750344

3233350 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 87669b62-390e-4838-ad28-b022e467f124
Approved on: 2024/4/22
Published on: 2024/4/22

HGVS expressions

NM_000329.3:c.16G>T
NC_000001.11:g.68448702C>A
CM000663.2:g.68448702C>A
NC_000001.10:g.68914385C>A
CM000663.1:g.68914385C>A
NC_000001.9:g.68686973C>A
NG_008472.1:g.6258G>T
NG_008472.2:g.6258G>T
ENST00000262340.6:c.16G>T
ENST00000262340.5:c.16G>T
NM_000329.2:c.16G>T

Pathogenic

Met criteria codes 3

PP4_Moderate PM2_Supporting PVS1

Not Met criteria codes 1

PM3

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.16G>T (p.Glu6Ter) is a frameshift variant that introduces a premature stop codon into exon 2 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 diagnosis with Leber congenital amaurosis (0.5 pts, PMID: 25257057) and significant, documented improvement of retinal sensitivity by dark-adapted perimetry and microperimetry after treatment with RPE65 gene therapy (8 pts, PMID: 25938638), which together are highly specific for RPE65-related recessive retinopathy (total 8.5 pts, PP4_Moderate). This variant has been reported in at least 1 proband with

early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state with the NM_000329.3(RPE65):c.499G>T (p.Asp167Tyr) variant suspected but not confirmed in trans (PMID: 25257057). However, the proband was not counted for PM3 in order to avoid circularity. 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 PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis with Leber congenital amaurosis (0.5 pts, PMID: 25257057) and significant, documented improvement of retinal sensitivity by dark-adapted perimetry and microperimetry after treatment with RPE65 gene therapy (8 pts, PMID: 25938638), which together are highly specific for RPE65-related recessive retinopathy (total 8.5 pts, PP4_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PVS1	✔	This is a [nonsense / frameshift] variant that introduces a premature stop codon into exon 2 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).

Not Met criteria codes

PM3	✖	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state with the NM_000329.3(RPE65):c.499G>T (p.Asp167Tyr) variant suspected but not confirmed in trans (PMID: 25257057). However, the proband was not counted for PM3 in order to avoid circularity.

Curation History

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