

Variant: *NM_000329.3(RPE65):c.993G>A (p.Trp331Ter)*

Version: 1.0

CA340744580 [↗](#)

973960 (ClinVar) [↗](#)

Gene: RPE65 ([HGNC:6121](#))

Condition: RPE65-related recessive retinopathy ([MONDO:0100368](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 9b8e106b-3115-4a6d-8e5d-5dfe89a22783

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HGVS expressions

NM_000329.3:c.993G>A

NM_000329.3(RPE65):c.993G>A (p.Trp331Ter)

NC_000001.11:g.68438947C>T

CM000663.2:g.68438947C>T

NC_000001.10:g.68904630C>T

CM000663.1:g.68904630C>T

NC_000001.9:g.68677218C>T

NG_008472.1:g.16013G>A

NG_008472.2:g.16013G>A

ENST00000262340.6:c.993G>A

ENST00000262340.5:c.993G>A

NM_000329.2:c.993G>A

Pathogenic

Met criteria codes **5**

PVS1

PM3_Supporting

PP1

PP4

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

NM_000329.3(RPE65):c.993G>A (p.Trp331Ter) is a nonsense variant that introduces a premature stop codon into exon 9 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 present in gnomAD v.4.1.0 at a GrpMax allele frequency of 2.800e-7 with 2 alleles / 1179940 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). This variant has been reported in 1 proband with early-onset severe retinal dystrophy who harbored the variant in the homozygous state (0.5 points;

PMID: 31725702). This variant has also been reported in 1 proband with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state with NM_000329.3(RPE65):c.906_907del (p.Asn302LysfsTer17) (PMID: 26047050). This proband was not counted for this criterion (PM3) to avoid circularity. (0.5 total points, PM3_Supporting). At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts) with nystagmus (1 pt), hyperopia, granular white/gray pigment in mid-peripheral retina (2 pts), and extinguished rod (0.5 pts) and cone (1 pt) ERG. Screening of a gene panel with 163 genes did not reveal any additional variants of interest (2 pts). Together these phenotypes are specific for RPE65-related recessive retinopathy (total 7 points, PMID: 260 47050, PP4). 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: 26047050). 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, PM3_Supporting, and PP1. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PVS1			This is a nonsense variant that introduces a premature stop codon into exon 9 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).
PM3_Supporting			This variant has been reported in 1 proband with early-onset severe retinal dystrophy who harbored the variant in the homozygous state (0.5 points; PMID: 31725702). This variant has also been reported in 1 proband with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state with NM_000329.3(RPE65):c.906_907del (p.Asn302LysfsTer17) (PMID: 26047050). This proband was not counted for this criterion to avoid circularity. (0.5 total points, PM3_Supporting).
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: 26047050)
PP4			At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts) with nystagmus (1 pt), hyperopia, granular white/gray pigment in mid-peripheral retina (2 pts), and extinguished rod (0.5 pts) and cone (1 pt) ERG. Screening of gene panel with 163 genes did not reveal any additional variants of interest (2 pts). Together they are specific for RPE65-related recessive retinopathy (total 7 points, PMID: 260 47050, PP4).
PM2_Supporting			This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 2.800e-7 with 2 alleles / 1179940 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).

Curation History

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