The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000329.3(RPE65):c.200T>G (p.Leu67Arg)

Version: 1.0

CA340749010

1068757 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4d66b49c-5789-488a-9be7-7312b3695d19
Approved on: 2024-02-20
Published on: 2024-02-20

HGVS expressions

NM_000329.3:c.200T>G
NM_000329.3(RPE65):c.200T>G (p.Leu67Arg)
NC_000001.11:g.68446755A>C
CM000663.2:g.68446755A>C
NC_000001.10:g.68912438A>C
CM000663.1:g.68912438A>C
NC_000001.9:g.68685026A>C
NG_008472.1:g.8205T>G
NG_008472.2:g.8205T>G
ENST00000262340.6:c.200T>G
ENST00000262340.5:c.200T>G
NM_000329.2:c.200T>G

Pathogenic

Met criteria codes 5

PP4_Moderate | PM2_Supporting | PP3_Moderate | PM3_Strong | PP1

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.200T>G is a missense variant that causes substitution of leucine with arginine at position 67. This variant is present in gnomAD v.2.1.1 at a maximum allele frequency of 0.00005437, with 1 allele / 18392 total alleles in the East Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.596dup (p.Asn199LysfsTer?) or NM_000329.3(RPE65):c.893del (Lys298Asnfs*27) variant confirmed in trans, which

were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total pts, PMID: 34830511, PM3_Strong). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with genotyping by targeted exome sequencing finding no alternative cause of disease among 188 known inherited retinal degeneration genes (2 pts), onset before the age of 5 years (1 pt), reduced central visual acuity (1 pt), nystagmus (1 pt), hypo-autofluorescence (2 pts), and extinguished electroretinogram responses from rods (0.5 pts) and cones (1 pt), which together are highly specific for RPE65-related recessive retinopathy (9 pts, PMID: 34830511, PP4_Moderate). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative in two different families, with the variant present in the compound heterozygous state in both instances (PMID: 22509104, PMID: 23661369, PP1). The computational predictor REVEL gives a score of 0.98, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). 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: PM2_Supporting, PM3_Strong, PP1, PP3_Moderate, 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 has been genotyped by targeted exome sequencing that found no alternative cause of disease among 188 known inherited retinal degeneration genes (2 pts) and exhibited a diagnosis of Leber congenital amaurosis (0.5 pts), onset before the age of 5 years (1 pt), reduced central visual acuity (1 pt), nystagmus (1 pt), hypo-autofluorescence (2 pts), and extinguished rod (0.5 pts) and cone (1 pt) electroretinogram responses, which together are highly specific for RPE65-related recessive retinopathy (9 pts, PMID: 34830511, PP4_Moderate).
PM2_Supporting	✔	This variant is present in gnomAD v.2.1.1 at a maximum allele frequency of 0.00005437, with 1 allele / 18392 total alleles in the East Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.98, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.02 for splice acceptor gain, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM3_Strong	✔	This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.596dup (p.Asn199LysfsTer?) or NM_000329.3(RPE65):c.893del (Lys298Asnfs*27) variant confirmed in trans, which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 points, PMID: 34830511, PM3_Strong).
PP1	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative in two different families, with the variant present in the compound heterozygous state in both instances (PP1; PMID: 22509104, PMID: 23661369).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000329.3(RPE65):c.200T>G (p.Leu...	Pathogenic	RPE65-Related Recessive Retinopathy	2024-02-20	1.0	ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RPE65 Version 1.0.0	RPE65

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