

Variant: NM_000329.3(RPE65):c.1301C>A (p.Ala434Glu)

Version: 1.1

CA340742486 [↗](#)

850613 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 8da3ac20-f2f0-43e1-b08a-6d3d7773bda9

Approved on: Tue, 22 Sep 2026 00:00:00 +0000

Published on: Tue, 22 Sep 2026 00:00:00 +0000

HGVS expressions

NM_000329.3(RPE65):c.1301C>A (p.Ala434Glu)

NM_000329.3:c.1301C>A

NC_000001.11:g.68431319G>T

CM000663.2:g.68431319G>T

NC_000001.10:g.68897002G>T

CM000663.1:g.68897002G>T

NC_000001.9:g.68669590G>T

NG_008472.1:g.23641C>A

NG_008472.2:g.23641C>A

ENST00000262340.6:c.1301C>A

ENST00000262340.5:c.1301C>A

NM_000329.2:c.1301C>A

Likely Pathogenic

Met criteria codes **5**

PM3_Strong

PP1

PP3

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

[↗](#) **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.1301C>A is a missense variant encoding a substitution of alanine by glutamic acid at codon 434. This variant is present in gnomAD v.4.1.1 at a frequency of 8.475e-7, with 1/ 1179918 alleles in the European (non-Finnish) population, which is lower than the ClinGen LCA/eaRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). In the Middle Eastern genetic ancestry group, the frequency of 1/6062 alleles (0.0001650) is also lower than the threshold. This variant has been reported in at least 3 unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.1399C>G

(p.Pro467Ala) variant confirmed in trans (1 pt, PMID: 31273949), the NM_000329.3(RPE65):c.95-2A>T variant suspected in trans (0.5 pts, LOVD), or the NM_000329.3(RPE65):c.74C>T (p.Pro25Leu) variant suspected in trans (0.5 pts, PMID: 29033008) all of which were previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong). 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 (PMID: 31273949, PP1). The computational predictor REVEL gives a score of 0.769, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.644 and predicts a damaging effect on RPE65 function (PP3). At least one proband harboring this variant exhibits a phenotype including extinguished rod ERG responses (0.5 pts), fundus albipunctatus / white dots (2 pts), onset between birth and age 5 years (1 pt), evidence of cone involvement on ERG (1 pt), and night blindness (0.5 pts), which together are specific for RPE65-related recessive retinopathy (5 pts, PMID: 31273949, PP4). In summary, this variant meets the criteria to be classified as likely 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, and PP4. (VCEP specifications version 1.0.0.).

Met criteria codes

PM3_Strong			This variant has been reported in at least 3 unrelated probands with early-onset severe retinal dystrophy. One proband (PMID:31273949) is compound heterozygous (confirmed in trans) with the c.1399C>G; p.Pro467Ala variant, previously curated as Pathogenic by the LCA/eoRD VCEP (1 point). A second proband is reported in the LOVD database to be found with the c.95-2A>T variant, previously curated as Pathogenic by the LCA/eoRD VCEP. No confirmation of phase available. (0.5 points). A third proband is reported (PMID:29033008) found with p.Pro25Leu variant which does not have confirmation of phase but has been classified by the LCA/eoRD VCEP as Pathogenic (0.5 points) (2.0 total points, PM3_Strong.)
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: 31273949).
PP3			The computational predictor REVEL gives a score of 0.769, which is above the ClinGen LCA/eoRD VCEP threshold of ≥ 0.644 for PP3_Supporting and predicts a damaging effect on RPE65 function (PP3). The LCA/eoRD VCEP threshold for PP3_Moderate is 0.774 and is almost met. AlphaMissense analysis of the variant predicts "likely pathogenic" with a score of 0.9732.
PP4			Individual P01-II:2 had extinguished rod ERG responses (0.5 pts), fundus albipunctatus/white dots (2 pts), onset between birth and age 5 (1 pt), evidence of cone involvement on ERG (1 pt), and night blindness (0.5 pts) which together are specific for RPE65-related recessive retinopathy (5.0 points, PMID: 31273949, PP4).
PM2_Supporting			This variant is present in gnomAD v.4.1.1 at a frequency of 8.475e-7, with 1/ 1179918 alleles in the European (non-Finnish) population, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). In the Middle Eastern genetic ancestry group, the frequency of 1/6062 alleles (0.0001650) is also lower than the threshold.

Curation History 

▼

▼

Showing 1 to 2 of 2 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.