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# *Variant: NM_000329.3(RPE65):c.1418T>A (p.Val473Asp)*

Version: 1.6

*CA226515*

*98846 (ClinVar)*

**Gene**: RPE65 (HGNC:6121)
**Condition**: RPE65-related recessive retinopathy (MONDO:0100368)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** d1b42d5c-6dd4-4376-b088-49da0241c349
**Approved on**: 2026/8/20
**Published on**: 2026/8/20

## *HGVS expressions*

**NM_000329.3(RPE65):c.1418T>A (p.Val473Asp)**
**NM_000329.3:c.1418T>A**
NC_000001.11:g.68431097A>T
CM000663.2:g.68431097A>T
NC_000001.10:g.68896780A>T
CM000663.1:g.68896780A>T
NC_000001.9:g.68669368A>T
NG_008472.1:g.23863T>A
NG_008472.2:g.23863T>A
ENST00000262340.6:c.1418T>A
ENST00000262340.5:c.1418T>A
NM_000329.2:c.1418T>A

**Likely Pathogenic**

**Met criteria codes** 4

PM3_Strong PP4_Moderate PP3_Moderate PM2_Supporting

**Not Met criteria codes** 2

BA1 BS1

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.1418T>A is a missense variant that substitutes valine with arginine at position p.473. This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMID: 9501220, SCV001430890.1). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Pro363Thr variant confirmed in trans (1 point, VCEP member-provided data), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong). At least one patient harboring the variant exhibits a**

**phenotype including nondetectable ERG responses from rods (0.5 pts) and cones ( 1 pt), nyctalopia (0.5 pts), decreased central visual acuity (1 pt), symptomatic onset between birth and age 5 years (1 pt), light staring (1 pt), and positive response to RPE65 gene therapy (8 pts), which together are highly specific for RPE65-related recessive retinopathy (13 total points, VCEP member-provided data, PP4_Moderate). This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00002196, with 2 alleles / 91080 total alleles in the South Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). The computational predictor REVEL gives a score of 0.992, which is above the ClinGen LCA/eoRD VCEP PP3_Mod 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 a Likely Pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM3_Strong, PP4_Moderate, PM2_Supporting, and PP3_Moderate. (LCA/eoRD VCEP specifications version 1.0.0).**

**Met criteria codes**

| | | |
|---|---|---|
| **PM3_Strong** | ✔ | At least two patients meeting the minimum phenotype requirement harbor the p.Val473Asp variant in the homozygous state (PMID: 9501220, SCV001430890.1, 1 pt). An additional report of a homozygous patient is found in PMID: 27375040 and PMID: 19854499, but it is not clear that this patient is unrelated to the first. Two compound heterozygous patients have been described (VCEP members-provided data) harboring the variant in trans with the p.Pro363Thr variant, which has been previously classified as Likely Pathogenic by the ClinGen Leber congenital amaurosis / early-onset retinal dystrophy (2 pts) (3 pt, PM3_Strong). |
| **PP4_Moderate** | ✔ | At least one patient harboring the variant exhibited reduced or nondetectable rod ERG (required, 2 pts), decreased central visual acuity (1 pt), symptomatic onset between birth and age 5 years (1 pt), evidence of cone involvement on ERG (1 pt), light staring (1 pt), nyctalopia (1 pt), and positive response to RPE65 gene therapy (8 pts), exceeding the 8 phenotype points required for this criterion (VCEP member-provided data, PP4_Moderate). A second reported patient met the phenotype point threshold as well (PMID: 9501220). A third reported patient with the same genotype exhibited similar phenotypes, but it is not clear whether the patients from PMID: 9501220 and PMID: 27375040 are distinct. |
| **PP3_Moderate** | ✔ | The meta-predictor REVEL gives a score of 0.992, which is above the ClinGen LCA/eoRP VCEP PP3 threshold of >0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The computational splicing predictor SpliceAI indicates that the variant may impact splicing by disrupting a splice acceptor (change score 0.10) or triggering a splice donor gain (change score 0.08), although these are not high-confidence predictions. |
| **PM2_Supporting** | ✔ | This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00002196, with 2 alleles / 91080 total alleles in the South Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **BA1** | ✖ | This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.00002196, with 2 alleles / 91080 total alleles in the South Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). |
| **BS1** | ✖ | This variant is absent from gnomAD v2.1.1. |

## Curation History

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