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Variant: NM_000329.3:c.1444G>A

Version: 2.0

CA340741708

3233349 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 10569ccb-8c8f-48b5-9329-a7ddce2d86d6
Approved on: 2026/6/23
Published on: 2026/6/23

HGVS expressions

NM_000329.3:c.1444G>A
NC_000001.11:g.68431071C>T
CM000663.2:g.68431071C>T
NC_000001.10:g.68896754C>T
CM000663.1:g.68896754C>T
NC_000001.9:g.68669342C>T
NG_008472.1:g.23889G>A
NG_008472.2:g.23889G>A
ENST00000262340.6:c.1444G>A
ENST00000262340.5:c.1444G>A
NM_000329.2:c.1444G>A

Pathogenic

Met criteria codes 5

PM3_Strong | PP1 | PP3_Moderate | PM2_Supporting | PP4_Moderate

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.1444G>A (p.Asp482Asn) is a missense variant predicted to replace aspartic acid with asparagine at codon 482. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.1543C>T (p.Arg515Trp) or NM_000329.3(RPE65):c.806_809delinsTGGAGCCATGAAG (p.Ser269MetfsTer4) variants confirmed in trans, which were both previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PMID: 34830511, PMID: 33952291, PM3_Strong). One genotype was published twice by two independent groups, but it has only been counted once as it is not clear whether the two probands might be the

same or related individuals (PMID: 34830511, PMID: 33952291). At least one proband harboring this variant exhibits a phenotype including diagnosis of retinitis pigmentosa with symptomatic onset between birth and age five years (1 pt), severely decreased rod electroretinogram (0.5 pt), evidence of cone involvement on electroretinogram (1 pt), reduced central visual acuity (1 pt), white/yellow dots on color photography of the type seen in fundus albipunctatus in the context of severe retinal dysfunction (2 pt), night blindness (0.5 pts), and genotyping by next-generation sequencing gene panel of 586 IRD-related genes that did not provide an alternative explanation for visual impairment (2 pt), which together are highly specific for RPE65-related recessive retinopathy (8 points, PMID: 33952291, 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, with the variant present in the compound heterozygous state (PMID: 33952291, PP1). The computational predictor REVEL gives a score of 0.946, 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

PM3_Strong	✔	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.1543C>T (p.Arg515Trp) or NM_000329.3(RPE65):c.806_809delinsTGGAGCCATGAAG (p.Ser269MetfsTer4) variants confirmed in trans, which were both previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PMID: 34830511, PMID: 33952291, PM3_Strong). One genotype was published twice by two independent groups, but it has only been counted once as it is not clear whether the two probands might be the same or related individuals (PMID: 34830511, PMID: 33952291).
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 (PMID: 33952291, PP1).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.946, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of retinitis pigmentosa with symptomatic onset between birth and age five years (1 pt), severely decreased rod electroretinogram (0.5 pt), evidence of cone involvement on electroretinogram (1 pt), reduced central visual acuity (1 pt), white/yellow dots on color photography of the type seen in fundus albipunctatus in the context of severe retinal dysfunction (2 pt), night blindness (0.5 pts), and genotyping by next-generation sequencing gene panel of 586 IRD-related genes that did not provide an alternative explanation for visual impairment (2 pt), which together are specific for RPE65-related recessive retinopathy (8 points, PMID: 33952291, PMID: 34830511, PP4_Moderate).

Curation History

Showing 1 to 2 of 2 rows

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