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Variant: NM_000329.3(RPE65):c.571A>G (p.Asn191Asp)

Version: 1.0

CA340747062

973956 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: c7f701ad-7569-48e7-9c8a-c87825cb1fad
Approved on: 2025/6/30
Published on: 2025/6/30

HGVS expressions

NM_000329.3(RPE65):c.571A>G (p.Asn191Asp)
NM_000329.3:c.571A>G
NC_000001.11:g.68440925T>C
CM000663.2:g.68440925T>C
NC_000001.10:g.68906608T>C
CM000663.1:g.68906608T>C
NC_000001.9:g.68679196T>C
NG_008472.1:g.14035A>G
NG_008472.2:g.14035A>G
ENST00000262340.6:c.571A>G
ENST00000262340.5:c.571A>G
NM_000329.2:c.571A>G

Likely Pathogenic

Met criteria codes 5

PM3 PP3_Moderate 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.571A>G (p.Asn191Asp) is a missense variant predicted to replace asparagine with aspartic acid at amino acid p.191. This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.000001830, with 6 alleles / 1179954 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 at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.440_441del (p.Thr147ArgfsTer9) variant confirmed in trans, which was previously classified

pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PMID: 40087508, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts, confirmed by clinician communication) before the age of 5 years (1 pt), reduced best-corrected visual acuity (1 pt), nystagmus (1 pt), and decreased electroretinogram responses (0.5 pts), which together are specific for RPE65-related recessive retinopathy (total 4 points, PMID: 40087508, 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: 40087508). The computational predictor REVEL gives a score of 0.935, 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 0.01, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. 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, PP1, PP3_Moderate, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000329.3(RPE65):c.440_441del (p.Thr147ArgfsTer9) variant confirmed in trans, which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PMID: 40087508, PM3).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.935, 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 0.01, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
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: 40087508).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts, confirmed by clinician communication) before the age of 5 years (1 pt), reduced best-corrected visual acuity (1 pt), nystagmus (1 pt), and decreased electroretinogram responses (0.5 pts), which together are specific for RPE65-related recessive retinopathy (total 4 points, PMID: 40087508, PP4).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.000001830, with 6 alleles / 1179954 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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