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Variant: NM_000329.3(RPE65):c.311G>A (p.Gly104Asp)

Version: 1.0

CA340748262

2202769 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3c2fa9e4-3081-46e0-8dbc-e9dacd065453
Approved on: 2025/6/11
Published on: 2025/6/11

HGVS expressions

NM_000329.3(RPE65):c.311G>A (p.Gly104Asp)
NM_000329.3:c.311G>A
NC_000001.11:g.68444818C>T
CM000663.2:g.68444818C>T
NC_000001.10:g.68910501C>T
CM000663.1:g.68910501C>T
NC_000001.9:g.68683089C>T
NG_008472.1:g.10142G>A
NG_008472.2:g.10142G>A
ENST00000262340.6:c.311G>A
ENST00000262340.5:c.311G>A
NM_000329.2:c.311G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM3 PP4 PP3_Moderate

Not Met criteria codes 1

PM5

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.311G>A (p.Gly104Asp) is a missense variant resulting in replacement of glycine by aspartic acid at amino acid 104. Another missense variant in the same codon, NM_000329.3(RPE65):c.310G>A (p.Gly104Ser), has been reported in relation to RPE65-related recessive retinopathy (PMID: 26667666), however, the SpliceAI score of 0.01 for the NM_000329.3(RPE65):c.311G>A (p.Gly104Asp) variant and the score of 0.29 for the NM_000329.3(RPE65):c.310G>A (p.Gly104Ser) comparison variant were not within 10% of one another, so PM5 is not met. This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.000000847, with 1 allele /

1,180,012 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 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.118G>A (p.Gly40Ser) variant suspected in trans (0.5 points, PMID: 19117922) or the NM_000329.3(RPE65):c.272G>A (p.Arg91Gln) variant confirmed in trans (1 point, PMID: 34830511, PMID: 25356976), both of which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1.5 total points, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of early onset severe retinal dystrophy (0.5 pts) with onset of night blindness (0.5 pts) at age 3 years (1 pt), reduced central visual acuity (1 pt), and genotyping by a targeted exome sequencing panel of 188 known inherited retinal degeneration genes (2 pts), which together are specific for RPE65-related recessive retinopathy (total 5 points, PMID: 34830511, PP4). The computational predictor REVEL gives a score of 0.962, 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, PP3_Moderate, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.000000847, with 1 allele / 1,180,012 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).
PM3	✔	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.118G>A (p.Gly40Ser) variant suspected in trans (0.5 points, PMID: 19117922) or the NM_000329.3(RPE65):c.272G>A (p.Arg91Gln) variant confirmed in trans (1 point, PMID: 34830511, PMID: 25356976), both of which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1.5 total points, PM3).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of early onset severe retinal dystrophy (0.5 pts) with onset of night blindness (0.5 pts) at age 3 years (1 pt), reduced central visual acuity (1 pt), and genotyping by a targeted exome sequencing panel of 188 known inherited retinal degeneration genes (2 pts), which together are specific for RPE65-related recessive retinopathy (total 5 points, PMID: 34830511, PP4).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.962, 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.

Not Met criteria codes

PM5	✖	Another missense variant in the same codon, NM_000329.3(RPE65):c.310G>A (p.Gly104Ser), has been reported in relation to RPE65-related recessive retinopathy (PMID: 26667666), however, the SpliceAI score of 0.01 for the NM_000329.3(RPE65):c.311G>A (p.Gly104Asp) variant and the score of 0.29 for the NM_000329.3(RPE65):c.310G>A (p.Gly104Ser) comparison variant were not within 10% of one another, so PM5 is not met.

Curation History

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