The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000329.3(RPE65):c.119G>A (p.Gly40Asp)

Version: 1.0

CA340749254

2432988 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 98cbde8d-3eb6-45b7-aa5c-beb3b701aea4
Approved on: Tue, 22 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000329.3:c.119G>A
NM_000329.3(RPE65):c.119G>A (p.Gly40Asp)
NC_000001.11:g.68446836C>T
CM000663.2:g.68446836C>T
NC_000001.10:g.68912519C>T
CM000663.1:g.68912519C>T
NC_000001.9:g.68685107C>T
NG_008472.1:g.8124G>A
NG_008472.2:g.8124G>A
ENST00000262340.6:c.119G>A
ENST00000262340.5:c.119G>A
NM_000329.2:c.119G>A

Likely Pathogenic

Met criteria codes 6

PP3_Moderate | PM3 | PM5 | 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*
- **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.119G>A (p.Gly40Asp) is a missense variant predicted to replace glycine with aspartate at position 40. This variant is present in gnomAD v.4.1.1 with an allele frequency of 1/1180032 alleles in the European (non-Finnish) 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 0.989, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and predicts a damaging effect on RPE65 function (PP3_Moderate). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5

points, PMID: 28418496). This variant has also been reported in 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the RPE65 c.370C>T (p.Arg124Ter) variant suspected in trans (0.5 points, PMIDs: 31630094, 34830511), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PM3). 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 homozygous state (PP1; PMID: 28418496). At least one proband harboring this variant exhibits a phenotype including macular dystrophy (0.5 pts), congenital night blindness (0.5 pts) and onset of night blindness before age 1 (1 pt) whose testing included a panel of 188 known inherited retinal degeneration genes (2 pts), which together are specific for RPE65-related recessive retinopathy (4 points, PMID: 34830511, PP4). Another missense variant in the same codon NM_000329.3(RPE65):c.118G>A (p.Gly40Ser) has been classified as pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PM5_Supporting, PMID: 25257057, PMID: 33608557). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants. 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, PM5_Supporting, and PP4. (VCEP specifications version 1.0.0)

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.989, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and predicts a damaging effect on RPE65 function (PP3).
PM3	✔	This variant has been reported in at least 1 proband(s) with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 point(s), PMID: 28418496). This variant has also been reported in at least 1 proband(s) with early-onset severe retinal dystrophy who was compound heterozygous with the RPE65 c.370C>T (p.Arg124Ter) variant suspected in trans (0.5 points, PMIDs: 31630094, 34830511), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total points, PM3_Supporting).
PM5	✔	Another missense variant in the same codon NM_000329.3(RPE65):c.118G>A (p.Gly40Ser) has been classified as pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PM5, PMID: 25257057, PMID: 33608557). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants.
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 homozygous state (PP1; PMID: 28418496).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including macular dystrophy (0.5 pts), congenital night blindness (0.5 pts) and onset of night blindness younger than 1 year old (1 pts) who's testing included a panel of 188 known inherited retinal degeneration genes (2 pts), which together are specific for RPE65-related recessive retinopathy (4 points, PMID: 34830511, PP4).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of -, with 1/1180032 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

Showing 1 to 1 of 1 rows

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