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Variant: NM_000329.3:c.137G>A

Version: 1.0

CA23577160

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 49d41313-de36-426a-9803-666f66b5674f
Approved on: 2026/1/15
Published on: 2026/1/16

HGVS expressions

NM_000329.3:c.137G>A
NC_000001.11:g.68446818C>T
CM000663.2:g.68446818C>T
NC_000001.10:g.68912501C>T
CM000663.1:g.68912501C>T
NC_000001.9:g.68685089C>T
NG_008472.1:g.8142G>A
NG_008472.2:g.8142G>A
ENST00000262340.6:c.137G>A
ENST00000262340.5:c.137G>A
NM_000329.2:c.137G>A

Likely Pathogenic

Met criteria codes 4

PM3_Strong | PM2_Supporting | PP1 | PP3_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.137G>A (p.Gly46Glu) is a missense variant that replaces the glycine at position p.46 with glutamic acid. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.98, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). This variant has been reported in 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Arg91Gln variant confirmed in trans (PMIDs: 32865313, 30268864), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 point). A second proband was compound heterozygous with the p.Tyr122Ter variant confirmed in trans (unpublished), which was previously classified likely

pathogenic by the ClinGen LCA / eoRD VCEP (1 point). (2 total points, PM3_Strong.) The variant has also 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:32865313). 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, PP3_Moderate, PP1, and PM3_Strong. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3_Strong	✔	This variant has been reported in 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Arg91Gln variant confirmed in trans (PMIDs: 32865313, 30268864), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 point). A second proband was compound heterozygous with the p.Tyr122Ter variant confirmed in trans (unpublished), which was previously classified likely pathogenic by the ClinGen LCA / eoRD VCEP (1 point). (2 total points, PM3_Strong.)
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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:32865313).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.98, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Curation History

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