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Variant: NM_000329.3(RPE65):c.419G>A (p.Gly140Glu)

Version: 1.1

CA340747862

467827 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: aa8a7955-4499-4f72-b2ec-e1e2f9783515
Approved on: 2026/8/20
Published on: 2026/8/20

HGVS expressions

NM_000329.3(RPE65):c.419G>A (p.Gly140Glu)
NM_000329.3:c.419G>A
NC_000001.11:g.68444607C>T
CM000663.2:g.68444607C>T
NC_000001.10:g.68910290C>T
CM000663.1:g.68910290C>T
NC_000001.9:g.68682878C>T
NG_008472.1:g.10353G>A
NG_008472.2:g.10353G>A
ENST00000262340.6:c.419G>A
ENST00000262340.5:c.419G>A
NM_000329.2:c.419G>A

Likely Pathogenic

Met criteria codes 4

PM3_Strong PP3_Moderate PP4_Moderate PM2_Supporting

Not Met criteria codes 3

BA1 BS1 BP4

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.419G>A is a missense variant causing substitution of glycine by glutamic acid at position 140. 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: 30870047). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.242G>T (p.Arg81Ile) and NM_000329.3(RPE65):c.1338G>T (p.Arg446Ser) variants confirmed in trans (2 points, PMID: 30870047), which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2.5 total points,

PM3_Strong). At least one proband harboring this variant exhibits a phenotype including diagnosis with Leber congenital amaurosis (0.5 pts) by exome sequencing that did not provide an alternative explanation for visual impairment (2 pts), onset at 1 month of age (1 pt), undetectable ERG responses from rods (0.5 pts) and cones (1 pt), nyctalopia (0.5 pts), reduced visual acuity (1 pt), light gazing (1 pt), RPE mottling (0.5 pts), optic nerve pallor (0.5 pt), nystagmus (1 pt), and pigmentary retinopathy with attenuated vessels (0.5 pt), which together are highly specific for RPE65-related recessive retinopathy (10 total points, PMID: 30870047, PP4_Moderate). This variant is present in gnomAD v.4.1.1 at allele frequency of 0.00001425 , with 23/ 1614004 total alleles 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 0.847, 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 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_Strong, PP3_Moderate, and PP4_Moderate. (LCA/eoRD VCEP specifications version 1.0.0).

Met criteria codes

PM3_Strong	✔	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: 30870047). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.242G>T (p.Arg81Ile) and NM_000329.3(RPE65):c.1338G>T (p.Arg446Ser) variants confirmed in trans (2 points, PMID: 30870047), which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2.5 total points, PM3_Strong). This variant has also been reported in an additional proband with retinitis pigmentosa who was compound heterozygous with the NM_000329.2(RPE65):c.292_311del (p.Ile98Hisfs) variant confirmed in trans (PMID: 28181551), however phenotypic details were not sufficient for inclusion in this code.
PP3_Moderate	✔	The meta-predictor REVEL gives a score of 0.847, which is above the ClinGen LCA/eoRP VCEP PP3 threshold of >0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PP4_Moderate	✔	This variant has been found by whole exome in a Leber congenital amaurosis patient without another cause of visual impairment (2 pt) with onset at 1 month of age (1 pt), undetectable rod ERG responses (required, 1 pt), nyctalopia (required, 1 pt), reduced visual acuity (1 pt), light gazing (1 pt), RPE mottling (0.5 pts), undetectable cone ERG responses (1 pt), optic nerve pallor (0.5 pt), nystagmus (1 pt), and pigmentary retinopathy with attenuated vessels (0.5 pt) (PMID: 30870047, PP4_Moderate).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.1 at allele frequency of 0.00001425 , with 23/ 1614004 total alleles which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).

Not Met criteria codes

BA1	✖	The Popmax FIltering AF for this variant in gnomAD 2.1.1 is 0.00003893, which is lower than the ClinGen LCA / eoRD threshold (>0.00816) for this criterion.
BS1	✖	The Popmax FIltering AF for this variant in gnomAD 2.1.1 is 0.00003893, which is lower than the ClinGen LCA / eoRD threshold (>0.000816) for this criterion.
BP4	✖	The meta-predictor REVEL gives a score of 0.847, which is above the ClinGen LCA/eoRP VCEP BP4 threshold of <0.3, while SpliceAI does not identify a suspected splicing defect. The computational evidence fails to meet this criterion.

Curation History

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