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Variant: NM_000329.3(RPE65):c.1249G>C (p.Glu417Gln)

Version: 2.0

CA226499

98835 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5bfcb761-d2e0-48a1-9cbc-eb413e453bac
Approved on: 2026/8/20
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HGVS expressions

NM_000329.3(RPE65):c.1249G>C (p.Glu417Gln)
NM_000329.3:c.1249G>C
NC_000001.11:g.68431371C>G
CM000663.2:g.68431371C>G
NC_000001.10:g.68897054C>G
CM000663.1:g.68897054C>G
NC_000001.9:g.68669642C>G
NG_008472.1:g.23589G>C
NG_008472.2:g.23589G>C
ENST00000262340.6:c.1249G>C
ENST00000262340.5:c.1249G>C
NM_000329.2:c.1249G>C

Pathogenic

Met criteria codes 6

PP3_Moderate PM1 PM3 PP4_Moderate PM2_Supporting PS3_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.1249G>C is a predicted missense variant substituting glutamic acid with glutamine at position p.417, which is located within the active site, a well-characterized functional domain required for enzymatic activity (PM1, PMID: 34492281).The computational predictor REVEL gives a score of 0.954, which is above the ClinGen LCA / eoRD VCEP PP3 threshold of >0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). In addition, the splicing impact predictor SpliceAI gives a score of 0.24 for acceptor gain, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing. The total

Grpmax allele frequency in gnomAD v4.1.1 is 6.8x10-7 (3/1179896 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 homozygous for the variant (0.5 points, PMID: 11462243, PMID: 20079931). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the c.11+5G>A variant confirmed in trans (1 point, VCEP member-provided data), 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 that is highly specific for RPE65-related recessive retinopathy (9 total points, VCEP member-provided data, PP4_Moderate). The variant exhibited 1-2% enzymatic activity in a retinoid isomerase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PS3_Supporting, PMID: 26427455, PMID: 16150724). In summary, this variant meets the criteria to be classified as Pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: PM1, PS3_supporting, PM2_Supporting, PM3, PP3_Moderate, and PP4_Moderate. (LCA/eoRD VCEP specifications version 1.0.0).

Met criteria codes

PP3_Moderate	✔	The meta-predictor REVEL gives a score of 0.954, which is above the ClinGen LCA/eoRD VCEP PP3 threshold of >0.773 and predicts a damaging effect on RPE65 function. In addition, SpliceAI predicts a splice acceptor gain with a change score of 0.24 (PP3_Moderate).
PM1	✔	This variant is a missense substitution at Glu417, which is located within the active site, a well-characterized functional domain required for enzymatic activity (PM1, PMID: 34492281).
PM3	✔	This variant has been observed in a compound heterozygous VCEP member-provided case, meeting the phenotype requirement for either severely reduced or absent rod response by ERG or congenital night blindness, in trans with the c.11+5G>A variant (classified Pathogenic by the VCEP), (1 pt, PM3). This variant has also been observed in a homozygous state in an affected LCA proband (0.5 pts, PMID: 11462243). A second report of an LCA-affected individual with the same genotype (PMID: 20079931) may or may not be related to the first. One patient has been scored (0.5 pt) with the VCEP-recommended assumption that the LCA diagnosis confirms the presence of a required phenotype (severely decreased rod ERG or congenital night blindness). The variant has also been observed in another VCEP member-provided case in trans with the NM_000329.3(RPE65):c.880A>G (p.Lys294Glu) variant, but has not been considered in this direction to avoid circularity (1.5 total points, PM3).
PP4_Moderate	✔	At least three probands harboring this variant have been supported, however, two of them (PMID: 20079931, PMID: 11462243) do not provide sufficient phenotypic details about the affected probands for this criterion. The VCEP member-provided case accumulated 9 total phenotype points, which was highly specific for recessive RPE65 retinopathy (VCEP member-provided data, PP4_Moderate).
PM2_Supporting	✔	The total Grpmax allele frequency in gnomAD v4.1.1 is 6.8x10-7 (3/1179896 alleles) in the European non-Finnish population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PS3_Supporting	✔	In PMID: 26427455 and PMID: 16150724, the variant exhibited a severe defect in enzymatic activity in assays with 8 or 11 total benign/pathogenic variants, respectively (PS3_Supporting).

Not Met criteria codes

BA1	✖	

The highest population minor allele frequency in gnomAD v4.1.1 is 0.00000254 (3/113312 alleles) in the European non-Finnish population, which is lower than the ClinGen LCA/eoRD VCEP threshold (>0.001) for BA1, failing to meet this criterion.

BS1	✖	The highest population minor allele frequency in gnomAD v4.1.1 is 0.00000254 (3/113312 alleles) in the European non-Finnish population, which is lower than the ClinGen LCA/eoRD VCEP threshold (>0.0001) for BS1, failing to meet this criterion.
BP4	✖	The meta-predictor REVEL gives a score of 0.954, which is above the ClinGen LCA/eoRD VCEP BP4 threshold of <0.3, while SpliceAI predicts a splice acceptor gain with a change score of 0.24. The computational evidence fails to meet this criterion.

Curation History

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