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Variant: NM_000329.3(RPE65):c.1399C>G (p.Pro467Ala)

Version: 1.0

CA340741972

1069898 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0bdf3eff-3307-4deb-b922-a33e0a747fba
Approved on: 2024/2/18
Published on: 2024/2/18

HGVS expressions

NM_000329.3:c.1399C>G
NM_000329.3(RPE65):c.1399C>G (p.Pro467Ala)
NC_000001.11:g.68431116G>C
CM000663.2:g.68431116G>C
NC_000001.10:g.68896799G>C
CM000663.1:g.68896799G>C
NC_000001.9:g.68669387G>C
NG_008472.1:g.23844C>G
NG_008472.2:g.23844C>G
ENST00000262340.6:c.1399C>G
ENST00000262340.5:c.1399C>G
NM_000329.2:c.1399C>G

Pathogenic

Met criteria codes 6

PM2_Supporting | PP1 | PP4 | PS3_Supporting | PM3_Strong | PP3_Moderate

Not Met criteria codes 1

BS1

Evidence Links 1

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.1399C>G is a missense variant causing substitution of proline by alanine at position 467. This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.00001898, with 2 alleles / 18384 total alleles in the East Asian 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 the NM_000329.3(RPE65):c.998+1G>A or NM_000329.3(RPE65):c.130C>T (p.Arg44Ter) variants confirmed in trans (PMID: 31273949, PMID: 30996589), which were previously

classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong). At least one proband harboring this variant exhibits a phenotype including grey-white fundus albipunctatus-like changes (2 pts), genotyping by exome sequencing that did not provide an alternative explanation for visual impairment (2 pts), night blindness with onset before age 5 years (1 pt), extinguished rod ERG responses (0.5 pts), and severely reduced cone ERG responses (1 pt), which together are specific for RPE65-related recessive retinopathy (6.5 total points, PMID: 31273949, PP4). Two other probands also meet the PP4 criteria including extinguished ERG, night blindness with onset in early childhood as well as additional consistent features such as white dot deposits in the mid-peripheral retina, and reduced visual acuity (PP4; PMID: 31273949). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative in 2 different families, with the variant present in the compound heterozygous state (PP1; PMID: 31273949). The computational predictor REVEL gives a score of 0.891, which is above the ClinGen LCA/eoRD VCEP threshold of >0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The variant exhibited 0% 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: 31580392). 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: PS3_Supporting, PM2_Supporting, PM3_Strong, PP1, 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.2.1.1 at a GrpMax allele frequency of 0.00001898, with 2 alleles / 18384 total alleles in the East Asian population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative in 2 different families, with the variant present in the compound heterozygous state (PP1; PMID: 31273949).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including grey-white fundus albipunctatus-like changes (2 pts), genotyping by exome sequencing that did not provide an alternative explanation for visual impairment (2 pts), night blindness with onset before age 5 years (1 pt), extinguished rod ERG responses (0.5 pts), and severely reduced cone ERG responses (1 pt), which together are specific for RPE65-related recessive retinopathy (6.5 total points, PMID: 31273949, PP4). Two other probands also meet the PP4 criteria including extinguished ERG, night blindness with onset in early childhood as well as additional consistent features such as white dot deposits in the mid-peripheral retina, and reduced visual acuity (PP4; PMID: 31273949).
PS3_Supporting	✔	The variant exhibited 0 % 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: 31580392). The variant exhibited 0 % 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: 31580392, Figure 5). PubMed:31580392
PM3_Strong	✔	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.998+1G>A and NM_000329.3(RPE65):c.130C>T (p.Arg44Ter) variants confirmed in trans (PMID: 31273949, PMID: 30996589), which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.891, which is above the ClinGen LCA/eoRD VCEP threshold of >0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Not Met criteria codes

BS1	ℹ	✖	The Popmax Filtering AF for this variant in gnomAD 2.1.1 is 0.00001898, which is lower than the ClinGen LCA/eoRD VCEP threshold ([>0.000816) for this criterion.

Curation History

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