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Variant: NM_000329.3(RPE65):c.499G>T (p.Asp167Tyr)

Version: 2.0

CA226557

98873 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: d53c7ff1-c734-4ed0-8666-65e7b2f4cda9
Approved on: 2024/7/23
Published on: 2024/7/23

HGVS expressions

NM_000329.3(RPE65):c.499G>T (p.Asp167Tyr)
NM_000329.3:c.499G>T
NC_000001.11:g.68440997C>A
CM000663.2:g.68440997C>A
NC_000001.10:g.68906680C>A
CM000663.1:g.68906680C>A
NC_000001.9:g.68679268C>A
NG_008472.1:g.13963G>T
NG_008472.2:g.13963G>T
ENST00000262340.6:c.499G>T
ENST00000262340.5:c.499G>T
NM_000329.2:c.499G>T

Pathogenic

Met criteria codes 5

PP3_Moderate | PP1 | PP4_Moderate | PM3_Strong | 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 1.0.0*
- **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.499G>T (p.Asp167Tyr) is a missense variant predicted to replace aspartic acid with tyrosine at position 167. This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.000007020 with 3 alleles / 113490 total 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 pts, PMID: 36547097). This variant has also been reported in at least 5 probands with early-onset severe retinal dystrophy who were compound

heterozygous with the NM_000329.3(RPE65):c.16G>T (p.Glu6Ter), NM_000329.3(RPE65):c.292_311del (p.Ile98HisfsTer26), NM_000329.3(RPE65):c.938A>G (p.His313Arg), or NM_000329.3(RPE65):c.778_785del (p.Asn260GlnfsTer18) variants suspected in trans (2 pts, PMID: 11095629, PMID: 35129589, PMID: 25257057), as well as the NM_000329.3(RPE65):c.11+5G>A variant confirmed in trans (1 pt, PMID: 35904185, PMID: 28224992), all of which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (3.5 total points, PM3_Strong). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts, PMID: 25257057), undetectable ERG response from rods (0.5 pts) and reduced ERG responses from cones (1 pt, PMID: 18441371) and significant, documented improvement of retinal sensitivity by dark-adapted perimetry and microperimetry after treatment with RPE65 gene therapy (8 pts, PMID: 25938638), which together are highly specific for RPE65-related recessive retinopathy (total 10 pts, PP4_Moderate). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through a proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PMID: 28224992, PP1). The computational predictor REVEL gives a score of 0.93, 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 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, PP1, PP3_Moderate, and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.93, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
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 (PMID: 28224992, PP1).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts, PMID: 25257057), undetectable ERG response from rods (0.5 pts) and reduced ERG responses from cones (1 pt, PMID: 18441371) and significant, documented improvement of retinal sensitivity by dark-adapted perimetry and microperimetry after treatment with RPE65 gene therapy (8 pts, PMID: 25938638), which together are highly specific for RPE65-related recessive retinopathy (total 10 pts, PP4_Moderate).
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 pts, PMID: 36547097). This variant has also been reported in at least 5 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_000329.3(RPE65):c.16G>T (p.Glu6Ter), NM_000329.3(RPE65):c.292_311del (p.Ile98HisfsTer26), NM_000329.3(RPE65):c.938A>G (p.His313Arg), or NM_000329.3(RPE65):c.778_785del (p.Asn260GlnfsTer18) variants suspected in trans (2 pts, PMID: 11095629, PMID: 35129589, PMID: 25257057), as well as the NM_000329.3(RPE65):c.11+5G>A variant confirmed in trans (1 pt, PMID: 35904185, PMID: 28224992), all of which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (3.5 total points, PM3_Strong). An additional proband harbored the NM_000329.3(RPE65):c.1580A>G (p.His527Arg) variant confirmed in trans, but was not counted for PM3 to avoid circularity (PMID: 35904185).
PM2_Supporting	✔	This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.000007020 with 3 alleles / 113490 total alleles 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

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