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Variant: NM_000329.3(RPE65):c.1543C>T (p.Arg515Trp)

Version: 1.0

CA226519

13120 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 62e2905f-cba8-449d-85c5-7f56947cd41a
Approved on: 2024-02-20
Published on: 2024-02-20

HGVS expressions

NM_000329.3:c.1543C>T
NM_000329.3(RPE65):c.1543C>T (p.Arg515Trp)
NC_000001.11:g.68429835G>A
CM000663.2:g.68429835G>A
NC_000001.10:g.68895518G>A
CM000663.1:g.68895518G>A
NC_000001.9:g.68668106G>A
NG_008472.1:g.25125C>T
NG_008472.2:g.25125C>T
ENST00000262340.6:c.1543C>T
ENST00000262340.5:c.1543C>T
NM_000329.2:c.1543C>T

Pathogenic

Met criteria codes 5

PP4_Moderate | PM2_Supporting | PM3_Strong | PP3_Moderate | PS3_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.1543C>T is a missense variant predicted to replace arginine with tryptophan at position 515. This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.000002980, with 2 alleles / 126782 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: 25495949). This variant has also been reported in at least 4 probands with early-onset severe retinal dystrophy who were compound

heterozygous with either the NM_000329.3(RPE65):c.1022T>C (p.Leu341Ser) (PMID: 34492281)), NM_000329.3(RPE65):c.1102T>C (p.Tyr368His) (PMID: 32032261), NM_000329.3(RPE65):c.1067dup (p.Asn356fs) (PMID: 35129589), or NM_000329.3(RPE65):c.130C>T (p.Arg44Ter) variant (PMID: 30025081) variants suspected in trans (2 pts), which were all 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 of Leber congenital amaurosis (0.5 pts) based on exome sequencing-based genotyping that did not provide an alternative explanation for visual impairment (2 pts), night blindness (0.5 pts) with onset during the first year of life (1 pt), attenuated retinal vessels (0.5 pts), macular atrophy (0.5 pts), bone spicule pigmentation (0.5 pts), non-recordable electroretinogram pattern in rod (0.5 pts) and cone (1 pt) responses, and decreased central visual acuity (1 pt), which together are highly specific for RPE65-related recessive retinopathy (8 total pts, PMID: 25495949, PP4_Moderate). The computational predictor REVEL gives a score of 0.935, 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 less than 10% 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 (PMID: 25752820, PS3_Supporting). 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, PP3_Moderate, and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PP4_Moderate	✔	At least one proband harboring this variant exhibits a diagnosis of Leber congenital amaurosis (0.5 pts) based on WES-based genotyping that did not provide an alternative explanation for visual impairment (2 pts), with a phenotype including night blindness (0.5 pts) with onset during the first year of life (1 pt), attenuated retinal vessels (0.5 pts), macular atrophy (0.5 pts) and isolated bone spicule pigmentation (0.5 pts), non-recordable ERG pattern in rod (0.5 pts) and cone (1 pt) responses, and decreased central visual acuity (1 pt), which together are highly specific for RPE65-related recessive retinopathy (8 total points, PMID: 25495949, PP4_Moderate).
PM2_Supporting	✔	NM_000329.3(RPE65):c.1543C>T is in gnomAD v2.1.1 with PopMax FAF of 0.000002980, which is below the ClinGen LCA / eoRD VCEP PM2 threshold of 2.0 x 10-4 (PM2_Supporting).
PM3_Strong	✔	This variant has been reported in at least 1 proband with Leber congenital amaurosis who was homozygous for the variant (0.5 pts, PMID: 25495949). This variant has also been reported in at least 4 probands with early-onset severe retinal dystrophy who were compound heterozygous suspected in trans with either the c.1022T>C p.Leu341Ser variant (PMID: 34492281, 0.5 pts), the c.1102T>C (p.Tyr368His) variant (PMID: 32032261, 0.5 pts), the c.1067dup (p.Asn356fs) variant (PMID: 35129589, 0.5 pts), or the c.130C>T (p.Arg44Ter) variant (PMID: 30025081, 0.5 pts), all of which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2.5 total points, PM3_Strong).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.935, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PS3_Supporting	✔	The variant c.1543C>T (p.Arg515Trp) exhibited less than 10% 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: 20043869 / PMID: 24849605 / PMID: 16150724 / PMID: 26427455 / PMID: 16828753).

Curation History

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