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Variant: NM_000329.3(RPE65):c.271C>T (p.Arg91Trp)

Version: 1.0

CA226531

13115 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 69b90ad5-3495-4624-b0dd-489f167402a1
Approved on: 2024-07-23
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HGVS expressions

NM_000329.3:c.271C>T
NM_000329.3(RPE65):c.271C>T (p.Arg91Trp)
NC_000001.11:g.68444858G>A
CM000663.2:g.68444858G>A
NC_000001.10:g.68910541G>A
CM000663.1:g.68910541G>A
NC_000001.9:g.68683129G>A
NG_008472.1:g.10102C>T
NG_008472.2:g.10102C>T
ENST00000262340.6:c.271C>T
ENST00000262340.5:c.271C>T
NM_000329.2:c.271C>T

Pathogenic

Met criteria codes 7

PS3_Supporting | PM3_Strong | PM2_Supporting | PM5 | PP1_Moderate | PP4_Moderate | PP3_Moderate

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.271C>T (p.Arg91Trp) is a missense variant predicted to replace arginine with tryptophan at position 91. This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.0001329, with 16 alleles / 74990 total alleles in the African / African-American 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 4 apparently unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMIDs: 35129589, 18722466). This variant has also been reported in at least 2 probands with early-onset severe

retinal dystrophy who were compound heterozygous with either the NM_000329.3(RPE65):c.11+5G>A or NM_000329.3(RPE65):c.272G>A (p.Arg91Gln) variants suspected in trans (1 point, PMIDs: 35129589, 33952291), both of which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong). At least one proband harboring this variant was genotyped by next-generation sequencing analysis of 586 candidate genes which did not provide an alternative explanation for visual impairment (2 pts) and exhibits a phenotype including congenital onset (1 pt), abnormal best corrected visual acuity test (1 pt), mild myopia, extinguished scotopic (0.5 pts) and photopic (1 pt) ERG responses, bone spicule pigmentation of the fundus (0.5 pts), white or yellow dots in fundus (2 pts), and nystagmus (1 pt), which together are highly specific for RPE65-related recessive retinopathy (9 total points, PMID: 31925606, PP4_Moderate). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PMID: 31925606, PP1_Moderate). The computational predictor REVEL gives a score of 0.852, which is above the ClinGen LCA/eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.22, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and predicts a damaging impact on splicing. Another missense variant in the same codon, NM_000329.3(RPE65):c.272G>A (p.Arg91Gln), has been classified as pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PM5). Splicing predictions using SpliceAI are equivalent for both of these variants. 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 (PMID: 16754667, 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: PM2_Supporting, PM3_strong, PP4_moderate, PP1_moderate, PP3_moderate, PM5, and PS3_supporting. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

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: 16754667).
PM3_Strong ✔	This variant has been reported in at least 4 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMIDs: 35129589, 18722466). This variant has also been reported in at least 2 proband(s) with early-onset severe retinal dystrophy who were compound heterozygous with the variants c.11+5G>A and c.272G>A (p.Arg91Gln), suspected in trans (1 point, PMIDs: 35129589, 33952291), which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong).
PM2_Supporting ✔	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.0001329, with 16 alleles / 74990 total alleles in the African / African-American population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PM5 ✔	Another missense variant in the same codon (p.Arg91Gln) has been classified as Pathogenic for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PM5). Splicing prediction using SpliceAI are equivalent for both of these variants.
PP1_Moderate ✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PP1_Moderate; PMID: 31925606).
PP4_Moderate ✔	At least one proband harboring this variant exhibits a phenotype including congenital onset (1 pt), abnormal best corrected visual acuity test (1 pt), Mild myopia, extinguished scotopic (0.5 pts) and photopic (1 pt) ERG responses, bone spicule pigmentation of the fundus (0.5 pts), white or yellow dots in fundus (2 pts), and nystagmus (1 pt), and genotyping performed by next-generation sequencing analysis of 586 candidate genes which did not provide an alternative explanation for visual impairment (2 pts). (PMID: 31925606). These 9 total phenotype points are sufficient to meet PP4_Moderate.

PP3_Moderate		✔	The splicing impact predictor SpliceAI gives a score of [0.22], which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and predicts a damaging impact on splicing (PP3). The computational predictor REVEL gives a score of [0.852], which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).

Curation History

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