The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000329.3(RPE65):c.1328T>C (p.Val443Ala)

Version: 1.1

CA340742376

870344 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: ddfaeffe-407e-4f2f-ac41-1df3ee46c3de
Approved on: 2026/8/20
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HGVS expressions

NM_000329.3(RPE65):c.1328T>C (p.Val443Ala)
NM_000329.3:c.1328T>C
NC_000001.11:g.68431292A>G
CM000663.2:g.68431292A>G
NC_000001.10:g.68896975A>G
CM000663.1:g.68896975A>G
NC_000001.9:g.68669563A>G
NG_008472.1:g.23668T>C
NG_008472.2:g.23668T>C
ENST00000262340.6:c.1328T>C
ENST00000262340.5:c.1328T>C
NM_000329.2:c.1328T>C

Likely Pathogenic

Met criteria codes 5

PM3 PP3_Moderate PP1 PP4_Moderate 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*
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:c.1328T>C(p.Val443Ala) is a predicted missense variant that replaces valine with alanine at position p.443 in RPE65. The computational predictor REVEL gives a score of 0.877, 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 0.27 for acceptor gain, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and predicts an impact on splicing. This variant has been reported in at least three probands an with early onset inherited retinal dystrophy. The first proband was diagnosed with early-onset severe retinal

dystrophy and is homozygous for the variant (0.5 points, VCEP member-provided data). The second proband was diagnosed with LCA and the variant is in the compound heterozygous state with the p.Tyr368His variant, which was previously classified as pathogenic by the ClinGen LCA / eoRD VCEP, phase is unknown (0.5 pts, PMID: 26626312). The third proband had a diagnosis of Severe Early Childhood Onset Retinal Dystrophy and harbors the variant in the compound heterozygous state with the p.Arg118Ser variant confirmed in trans (PMID: 20811047). However, the proband was not counted for PM3 in this case in order to avoid circularity (0 points). (1 pt total, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA or severe RP with onset in the first decade of life (0.5 pts), previous exome, genome or 100+ retinal dystrophy gene panel testing that did not provide an alternative explanation for visual impairment (2 pts), childhood night blindness, reduced visual acuity (1 pt), globally reduced autofluorescence (2 pts), optic nerve pallor (0.5 pts), pigmentary retinopathy with attenuated vessels (0.5 pts) posterior subcapsular cataract (0.5 pts), macular atrophy (0.5 pts), and decreased peripheral vision (1 pt), which together are highly specific for RPE65-related recessive retinopathy (8.5 total points, VCEP member-provided data, PP4_Moderate). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative (PMID: 20811047, PP1). This variant is present in gnomAD v.4.1.1 at a GrpMax allele frequency of 0.000005085, with 6 alleles / 1179866 total allele] in the European (non-Finnish) population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM2_Supporting, PM3, PP1, PP3_Moderate, and PP4_moderate. (LCA/eoRD VCEP specifications version 1.0.0).

Met criteria codes

PM3	✓	This variant has been reported in at least three probands an with early onset inherited retinal dystrophy. The first proband was diagnosed with early-onset severe retinal dystrophy and is homozygous for the variant (0.5 points, VCEP member-provided data). The second proband was diagnosed with LCA and the variant is in the compound heterozygous state with the p.Tyr368His variant, which was previously classified as pathogenic by the ClinGen Leber congenital amaurosis / early onset retinal dystrophy VCEP, phase is unknown (0.5 pts, PMID: 26626312). The third proband had a diagnosis of Severe Early Childhood Onset Retinal Dystrophy and harbors the variant in the compound heterozygous state with the p.Arg118Ser variant confirmed in trans (PMID: 20811047), however, this proband was not counted for PM3 in order to avoid circularity (0 points). (1 pt total, PM3 met).
PP3_Moderate	✓	The computational predictor REVEL gives a score of 0.877, 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 0.27 for acceptor gain, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and predicts an impact on splicing.
PP1	✓	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through at least 1 affected meiosis from 1 family, with the variant present in the compound heterozygous state (PP1; PMID: 20811047).
PP4_Moderate	✓	At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA or severe RP with onset in the first decade of life (0.5 pts), previous exome, genome or 100+ retinal dystrophy gene panel testing that did not provide an alternative explanation for visual impairment (2 pts), childhood night blindness, reduced visual acuity (1 pt), globally reduced autofluorescence (2 pts), optic nerve pallor (0.5 pts), pigmentary retinopathy with attenuated vessels (0.5 pts) posterior subcapsular cataract (0.5 pts), macular atrophy (0.5 pts), and decreased peripheral vision (1 pt), which together are highly specific for RPE65-related recessive retinopathy (8.5 total points, VCEP member-provided data, PP4_Moderate).
PM2_Supporting	✓	This variant is present in gnomAD v.4.1.1 at a Grpmax allele frequency of 0.000005085, with 6 alleles / 1,179,866 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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