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Variant: NM_000329.3(RPE65):c.434C>A (p.Ala145Asp)

Version: 1.1

CA340747756

3024117 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: bc545cdf-c331-4bcf-b50f-b561a1be3aee
Approved on: 2026/8/20
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HGVS expressions

NM_000329.3(RPE65):c.434C>A (p.Ala145Asp)
NM_000329.3:c.434C>A
NC_000001.11:g.68444592G>T
CM000663.2:g.68444592G>T
NC_000001.10:g.68910275G>T
CM000663.1:g.68910275G>T
NC_000001.9:g.68682863G>T
NG_008472.1:g.10368C>A
NG_008472.2:g.10368C>A
ENST00000262340.6:c.434C>A
ENST00000262340.5:c.434C>A
NM_000329.2:c.434C>A

Likely Pathogenic

Met criteria codes 5

PP3_Moderate | PP1 | PP4 | PM3_Strong | PM2_Supporting

Not Met criteria codes 1

PM5

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(RPE65):c.434C>A is a missense variant that causes substitution of alanine with aspartic acid at position p.145. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including a diagnosis of fundus albipunctatus (2 pts) with genotyping by exome sequencing without finding an alternative explanation for disease (2 pts), nyctalopia (0.5 pts), onset at age 3.3 years (1 pt), undetectable dark-adapted electroretinogram (0.5 pts), and severely reduced light-adapted electroretinogram (1 pt), which together are specific for RPE65-related recessive retinopathy (7 total pts, PMID: 31273949, PP4).

This variant has 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.200T>G (p.Leu67Arg) or the NM_000329.3(RPE65):c.1399C>G (p.Pro467Ala) variants confirmed in trans, which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 points, PMID: 23661369, PMID: 31273949, PM3_Strong). 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: 31273949, PP1). Two other missense variants in the same codon, NM_000329.3(RPE65):c.433G>A (p.Ala145Thr) (PMID: 26906952) and NM_000329.3(RPE65):c.433G>C (p.Ala145Pro) (PMID: 28224992) have been classified for RPE65-related recessive retinopathy by the ClinGen LCA / eoRD VCEP, however, the PM5 code has not been considered in order to avoid circularity. The computational predictor REVEL gives a score of 0.929, 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 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_Strong, PP1, PP3_Moderate, and PP4. (LCA/eoRD VCEP specifications version 1.0.0)

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.929, 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 fundus albipunctatus through at least 1 affected meiosis from 1 family, with the variant present in the compound heterozygous state with the p.Pro467Ala variant confirmed in trans (PP1; PMID: 31273949).
PP4	✔	At least two probands harboring this variant exhibit a phenotype specific for RPE65-related recessive retinopathy (PMID: 23661369, PMID: 31273949), one with a phenotype including nyctalopia (0.5 pts) and reduced visual acuity with childhood onset (1 pt), photophobia (1 pt), pigment deposits in the macula (0.5 pts), attenuation of retinal vessels (0.5 pts), and optic disc pallor (0.5 pts), which together are specific for RPE65-related recessive retinopathy (4 points, PP4).
PM3_Strong	✔	This variant has 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.200T>G (p.Leu67Arg) or the NM_000329.3(RPE65):c.1399C>G (p.Pro467Ala) variants confirmed in trans, which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PMID: 23661369, PMID: 31273949PM3, PM3_Strong).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (PM2_Supporting).

Not Met criteria codes

PM5	✖	Two other missense variants at the same codon have been reported in similarly affected individuals (NM_000329.3(RPE65):c.433G>A (p.Ala145Thr) in PMID: 26906952, and NM_000329.3(RPE65):c.433G>C (p.Ala145Pro) in PMID: 28224992). However, this variant has not been considered for the PM5 code in order to avoid circularity.

Curation History

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