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Variant: NM_000329.3(RPE65):c.515T>A (p.Val172Asp)

Version: 1.0

CA340747191

978981 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: c2cf9e30-17f3-46ed-8232-edd32499cae4
Approved on: 2025/3/31
Published on: 2025/3/31

HGVS expressions

NM_000329.3:c.515T>A
NM_000329.3(RPE65):c.515T>A (p.Val172Asp)
NC_000001.11:g.68440981A>T
CM000663.2:g.68440981A>T
NC_000001.10:g.68906664A>T
CM000663.1:g.68906664A>T
NC_000001.9:g.68679252A>T
NG_008472.1:g.13979T>A
NG_008472.2:g.13979T>A
ENST00000262340.6:c.515T>A
ENST00000262340.5:c.515T>A
NM_000329.2:c.515T>A

Likely Pathogenic

Met criteria codes 4

PP3_Moderate PP4 PM3 PM2_Supporting

Not Met criteria codes 1

PM4

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

The NM_000329.3(RPE65):c.515T>A (p.Val172Asp) variant is a missense variant in RPE65 causing a substitution of valine with aspartic acid at position 172. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.811, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the Arg91Trp variant confirmed in trans (1 point, PMIDs: 27874104), which was previously classified pathogenic by the ClinGen LCA / eoRD

VCEP (1 total point, PM3). At least one proband harboring this variant exhibits a phenotype including a clinical diagnosis of retinitis pigmentosa with detailed phenotype demonstrating early-onset severe retinal dystrophy including macular atrophy (0.5 pt), nystagmus (1 pt), symptomatic onset between birth and age five years (1 pt), pigmentary retinopathy with attenuated vessels (0.5 pt), optic atrophy (0.5 pt), decreased central visual acuity (1 pt), which together are specific for RPE65-related recessive retinopathy (4.5 points, PMID: 27874104, PP4). 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, PP3_Moderate, PM3, PP4 (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 0.811, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including a clinical diagnosis of retinitis pigmentosa with detailed phenotype demonstrating early-onset severe retinal dystrophy including macular atrophy (0.5 pt), nystagmus (1 pt), symptomatic onset between birth and age five years (1 pt), pigmentary retinopathy with attenuated vessels (0.5 pt), optic atrophy (0.5 pt), decreased central visual acuity (1 pt), which together are specific for RPE65-related recessive retinopathy (4.5 points, PMID: 27874104, PP4).
PM3	✔	This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the Arg91Trp variant confirmed in trans (1 point, PMIDs: 27874104), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (1 total point, PM3).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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