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Variant: NM_000329.3(RPE65):c.1445A>G (p.Asp482Gly)

Version: 1.0

CA902169

850287 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5abc6e2a-2e9c-4968-b121-191406d3312a
Approved on: 2025/3/27
Published on: 2025/3/27

HGVS expressions

NM_000329.3(RPE65):c.1445A>G (p.Asp482Gly)
NM_000329.3:c.1445A>G
NC_000001.11:g.68431070T>C
CM000663.2:g.68431070T>C
NC_000001.10:g.68896753T>C
CM000663.1:g.68896753T>C
NC_000001.9:g.68669341T>C
NG_008472.1:g.23890A>G
NG_008472.2:g.23890A>G
ENST00000262340.6:c.1445A>G
ENST00000262340.5:c.1445A>G
NM_000329.2:c.1445A>G

Likely Pathogenic

Met criteria codes 5

PM3 PP3_Moderate PP1 PP4 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 1.0.0*
- **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.1445A>G (p.Asp482Gly) variant is a missense variant predicted to replace aspartic acid with glycine at amino acid 482 in RPE65. This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.00006, with [4/64040 total alleles in the European, Finnish population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). The computational predictor REVEL gives a score of 0.974, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). Additionall, the splicing impact predictor SpliceAI gives a score of 0.69 for splice

donor gain, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing. This variant has been reported in at least 2 proband(s) with early-onset severe retinal dystrophy who were either compound heterozygous with the p.Tyr431Cys confirmed in trans (1 pt, Invitae-provided data) or with the p.Arg234* suspected in trans (0.5 points, VCEP member-provided data) which were previously classified pathogenic or likely pathogenic by the ClinGen LCA / eoRD VCEP (1.5 total points, PM3). In addition, this variant has been reported in another patient with early-onset severe retinal dystrophy and his similarly affected brother who were compound heterozygous with the p.Tyr431Cys variant suspected in trans (VCEP member-provided data). As it is possible that these this the same proband provided by Invitae, they were not counted for additional PM3 points. This variant has also been reported in one proband in who was compound heterozygous with the Tyr79His variant suspected in trans, but was not counted due to insufficient clinical information (PMID: 30268864). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through this proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; VCEP member-provided data). At least one proband harboring this variant exhibits a phenotype including nyctalopia (0.5), abnormal fundus appearance (2), optic nerve pallor (0.5), RPE mottling (0.5), symptomatic onset between birth and five years (1), decreased peripheral vision (1), abnormal color vision (1), and decreased central visual acuity (1), which together are specific for RPE65-related recessive retinopathy (7.5 points, VCEP member-provided data, 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/eoRP VCEP: PP3_Moderate, PM3, PM2_Supporting, PP1, PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023)

Met criteria codes

PM3	✔	This variant has been reported in at least 2 proband(s) with early-onset severe retinal dystrophy who were either compound heterozygous with the p.Tyr431Cys confirmed in trans (1 pt, Invitae-provided data) or with the p.Arg234* suspected in trans (0.5 points, VCEP member-provided data) which were previously classified pathogenic or likely pathogenic by the ClinGen LCA / eoRD VCEP (1.5 total points, PM3). In addition, this variant has been reported in another patient with early-onset severe retinal dystrophy and his similarly affected brother who were compound heterozygous with the p.Tyr431Cys variant suspected in trans (VCEP member-provided data). As it is possible that these this the same proband provided by Invitae, they were not counted for additional PM3 points. This variant has also been reported in one proband in who was compound heterozygous with the Tyr79His variant suspected in trans, but was not counted due to insufficient clinical information (PMID: 30268864).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.974, which is above the ClinGen LCA / eoRD VCEP threshold of ≥ 0.773 and predicts a damaging effect on RPE65 function (PP3_Moderate). Additionall, the splicing impact predictor SpliceAI gives a score of 0.69 for splice donor gain, which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing.
PP1	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through this proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; VCEP member-provided data).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including nyctalopia (0.5), abnormal fundus appearance (2), optic nerve pallor (0.5), RPE mottling (0.5), symptomatic onset between birth and five years (1), decreased peripheral vision (1), abnormal color vision (1), and decreased central visual acuity (1), which together are specific for RPE65-related recessive retinopathy (7.5 points, VCEP member-provided data, PP4).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.00006, with [4/64040 total alleles in the European, 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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