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Variant: NM_000180.4(GUCY2D):c.2927G>T (p.Arg976Leu)

Version: 1.0

CA226107

98581 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7cad45b2-1d7a-4730-8f40-0d330e6c3c30
Approved on: 2025/1/30
Published on: 2025/1/30

HGVS expressions

NM_000180.4(GUCY2D):c.2927G>T (p.Arg976Leu)
NM_000180.4:c.2927G>T
NC_000017.11:g.8015485G>T
CM000679.2:g.8015485G>T
NC_000017.10:g.7918803G>T
CM000679.1:g.7918803G>T
NC_000017.9:g.7859528G>T
NG_009092.1:g.17816G>T
ENST00000254854.5:c.2927G>T
ENST00000254854.4:c.2927G>T
NM_000180.3:c.2927G>T

Likely Pathogenic

Met criteria codes 6

PP4 | PM3_Supporting | PM1 | PP3_Moderate | PS3_Supporting | 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 GUCY2D 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_000180.4(GUCY2D):c.2927G>T (p.Arg976Leu) is a missense variant that replaces arginine with leucine at position p.976, which is located within the active site, a well-characterized functional domain that binds the GTP substrate and the Mg ion and is required for enzymatic activity (PM1, PMID: 9391039). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 total points, PMID: 10951519, PM3_Supporting). A second proband was not only homozygous for this variant but also for the NM_000180.4(GUCY2D):c.2766C>G (p.Tyr922Ter) variant, and so was not counted for the PM3 code (PMID: 24265693). At least one proband harboring this variant exhibits a

phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), severely reduced vision (1 pt) with onset from birth (1 pt), nystagmus (1 pt), unremarkable fundus, irregular pigmentation (0.5 pts), hypermetropia, electroretinogram responses below the detection limit from both rods (0.5 pts) and cones (1 pt), and macular atrophy, which together are specific for GUCY2D-related recessive retinopathy (total 5.5 points, PMID: 17525851, PP4). The computational predictor REVEL gives a score of 0.895, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 protein function (PP3_Moderate). The variant exhibited 0% enzymatic activity in a guanylate cyclase assay relative to the wild-type control, which is lower than the ClinGen LCA/eoRD VCEP PS3_Supporting threshold of ≤10% activity, indicating that it triggers a severe defect in protein function (PMID: 11328726, PS3_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for GUCY2D-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: PM1, PM2_Supporting, PM3_Supporting, PP4, PP3_Moderate, and PS3_Supporting. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PP4 ✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), severely reduced vision (1 pt) with onset from birth (1 pt), nystagmus (1 pt), unremarkable fundus, irregular pigmentation (0.5 pts), hypermetropia, electroretinogram responses below the detection limit from both rods (0.5 pts) and cones (1 pt), and macular atrophy, which together are specific for GUCY2D-related recessive retinopathy (total 5.5 points, PMID: 17525851, PP4).
PM3_Supporting ✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who were homozygous for the variant (0.5 total points, PMID: 10951519, PM3_Supporting). A second proband was not only homozygous for his variant but also for the NM_000180.4(GUCY2D):c.2766C>G (p.Tyr922Ter) variant, and so was not counted for the PM3 code (PMID: 24265693).
PM1 ✔	This variant is a missense substitution at Arg976, which is located within the active site, a well-characterized functional domain required that binds the GTP substrate and the Mg ion and is required for enzymatic activity (PM1, PMID: 9391039).
PP3_Moderate ✔	The computational predictor REVEL gives a score of 0.895, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.03 for donor gain, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PS3_Supporting ✔	The variant exhibited 0% enzymatic activity in a guanylate cyclase assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD VCEP PS3_Supporting threshold of ≤10% activity, indicating that it triggers a severe defect in protein function (PMID: 11328726, PS3_Supporting).
PM2_Supporting ✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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