

Variant: *NM_000180.4(GUCY2D):c.839C>G (p.Thr280Arg)*

Version: 1.0

CA287523615 [↗](#)

808220 (ClinVar) [↗](#)

Gene: GUCY2D ([HGNC:3000](#))

Condition: GUCY2D-related recessive retinopathy ([MONDO:0100453](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 897efc9b-c34f-4e7d-b398-d71cb148f5d2

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HGVS expressions

NM_000180.4:c.839C>G

NM_000180.4(GUCY2D):c.839C>G (p.Thr280Arg)

NC_000017.11:g.8003969C>G

CM000679.2:g.8003969C>G

NC_000017.10:g.7907287C>G

CM000679.1:g.7907287C>G

NC_000017.9:g.7848012C>G

NG_009092.1:g.6300C>G

ENST00000254854.5:c.839C>G

ENST00000254854.4:c.839C>G

NM_000180.3:c.839C>G

Likely Pathogenic

Met criteria codes **5**

PP1

PP3

PP4

PM3

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

The NM_000180.4(GUCY2D):c.839C>G (p.Thr280Arg) variant predicts the substitution of arginine for threonine at position p.280. While the REVEL score is indeterminate (0.58) and does not support a deleterious effect on protein structure, the splicing impact predictor SpliceAI gives a score of 0.46 which is above the ClinGen LCA/eoRD VCEP recommended threshold of ≥ 0.2 and predicts a damaging impact on splicing (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting) and has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant. (1 point, PMIDs: 2642740, 29068479, PM3). 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 homozygous state (PP1; PMID: 29068479). At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts), significantly reduced rod ERG (0.5 pts) and extinguished cone ERG (1 pt), decreased peripheral vision (1 pt) and decreased visual acuity (1 pt). The patient's OCT showed retinal structure preserved relative to vision loss (1 pt). (Total points 5.0, PP4). 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: PM3, PP1, PP3, PP4, PM2 supporting. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PP1			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 homozygous state (PP1; PMID: 29068479).
PP3			The splicing impact predictor SpliceAI gives a score of 0.46 which is above the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and predicts a damaging impact on splicing (PP3).
PP4			At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts), significantly reduced rod ERG (0.5 pts) and extinguished cone ERG (1 pt), decreased peripheral vision (1 pt) and visual acuity (1 pt). OCT showed retinal structure preserved relative to vision loss (1 pt). Total points 5.0, PP4. (Patient is undergoing gene therapy and may be considered for PP4_Moderate depending on the outcome.)
PM3			This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant. 1 point, PMIDs: 2642740, 29068479 (PM3)
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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