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Variant: NM_000180.4:c.2765A>G

Version: 1.0

CA397954276

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3f50dcf7-c21c-42a3-88df-605e6e0338a1
Approved on: 2025/1/31
Published on: 2025/1/31

HGVS expressions

NM_000180.4:c.2765A>G
NC_000017.11:g.8015047A>G
CM000679.2:g.8015047A>G
NC_000017.10:g.7918365A>G
CM000679.1:g.7918365A>G
NC_000017.9:g.7859090A>G
NG_009092.1:g.17378A>G
ENST00000254854.5:c.2765A>G
ENST00000254854.4:c.2765A>G
NM_000180.3:c.2765A>G

Likely Pathogenic

Met criteria codes 4

PP3_Moderate | PM3 | PM1_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.2765A>G (p.Tyr922Cys) is a missense variant that replaces tyrosine with cysteine at position p.922, which is located within the guanylate cyclase catalytic domain that exhibits intolerance to missense variation (PM1_Supporting). 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 harbored the variant in the compound heterozygous state confirmed in trans with the NM_000180.4(GUCY2D):c.2983C>T (p.Arg995Trp) variant, which was previously classified as likely pathogenic by the ClinGen LCA/eoRD VCEP (1 pt, PMID: 29844330, PM3). The computational predictor REVEL gives a score of 0.946 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 splicing impact predictor SpliceAI gives a score of 0.03 for splice donor

gain, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. 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: PM2_Supporting, PM1_Supporting, PM3, and PP3_Moderate. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.946 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 splice donor gain, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state confirmed in trans with the NM_000180.4(GUCY2D):c.2983C>T (p.Arg995Trp) variant, which was previously classified as likely pathogenic by the ClinGen LCA / eoRD VCEP (1 pt, PMID: 29844330, PM3).
PM1_Supporting	✔	This variant is a missense substitution at Tyr922, which is located within the guanylate cyclase catalytic domain that exhibits intolerance to missense variation (PM1_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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