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Variant: NM_000180.4(GUCY2D):c.2132C>T (p.Pro711Leu)

Version: 1.0

CA8366018

974639 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2d299d0b-fbf5-47cc-84f6-ba333a419de9
Approved on: 2025/1/30
Published on: 2025/1/30

HGVS expressions

NM_000180.4(GUCY2D):c.2132C>T (p.Pro711Leu)
NM_000180.4:c.2132C>T
NC_000017.11:g.8013121C>T
CM000679.2:g.8013121C>T
NC_000017.10:g.7916439C>T
CM000679.1:g.7916439C>T
NC_000017.9:g.7857164C>T
NG_009092.1:g.15452C>T
ENST00000254854.5:c.2132C>T
ENST00000254854.4:c.2132C>T
NM_000180.3:c.2132C>T

Likely Pathogenic

Met criteria codes 4

PM3_Supporting | PP3_Moderate | PP4_Moderate | 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.2132C>T (p.Pro711Leu) variant is predicted to replace the proline at position p.711 with leucine. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000006199, with 10 alleles / 1,613,180 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting). The computational predictor REVEL gives a score of 0.857, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 protein function (PP3_Moderate). At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5), present at birth (1 pt.), visual acuity of LP (light perception) (1 pt), visual field loss (1 pt), nystagmus (1 pt), photophobia (1 pt), non-recordable ERGs (1.5 pts),

and without alternative variants after large gene panel testing (2 pts). Together these are highly specific for GUCY2D-related recessive retinopathy (total 9 points, PMID: 23847139, PP4_Moderate). This variant has been reported in at least one proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, PMID: 23847139). This variant has also been reported in one proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Glu196Val variant suspected in trans (0 points, PMID:20683928), which has not been classified by the ClinGen LCA/eoRD VCEP (0.5 total points, PM3_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: PP3_Moderate, PP4_Moderate, PM3_Supporting, and PM2_Supporting.(VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PM3_Supporting	✔	This variant has been reported in at least one proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, PMID: 23847139). This variant has also been reported in one proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Glu196Val variant suspected in trans (0 points, PMID:20683928), which has not been classified by the ClinGen LCA / eoRD VCEP (0.5 total points, PM3_Supporting).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.857, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 function (PP3_Moderate).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5), present at birth (1 pt.), visual acuity of LP (light perception) (1 pt), visual field loss (1 pt), nystagmus (1 pt), photophobia (1 pt), non-recordable ERGs (1.5 pts), and without alternative variants after large gene panel testing (2 pts). Together these are highly specific for GUCY2D-related recessive retinopathy (total 9 points, PMID: 23847139, PP4_Moderate).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000006199, with 10 alleles / 1,613,180 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).

Curation History

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