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Variant: NM_000180.4(GUCY2D):c.725T>G (p.Val242Gly)

Version: 1.0

CA397945013

974634 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4a876cb6-7672-4b6b-9467-b01c61ec49b0
Approved on: 2026/9/9
Published on: 2026/9/9

HGVS expressions

NM_000180.4(GUCY2D):c.725T>G (p.Val242Gly)
NM_000180.4:c.725T>G
NC_000017.11:g.8003855T>G
CM000679.2:g.8003855T>G
NC_000017.10:g.7907173T>G
CM000679.1:g.7907173T>G
NC_000017.9:g.7847898T>G
NG_009092.1:g.6186T>G
ENST00000254854.5:c.725T>G
ENST00000254854.4:c.725T>G
NM_000180.3:c.725T>G

Likely Pathogenic

Met criteria codes 5

PM2_Supporting | PP1 | PP4 | PM3 | PP3_Moderate

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*
- **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.725T>G (p.Val242Gly) variant is a missense change that replaces valine with glycine at position p.242. It is present in gnomAD v.4.1.1 at a total allele frequency of 6.205e-7, with 1 allele /1611594 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 0.873, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on RETGC-1 protein function (PP3_Moderate). 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, PMID: 39939321 and VCEP member personal communication). This variant has also been reported in at least 1 proband with

early-onset severe retinal dystrophy who was compound heterozygous with the c.2660T>G p.Val887Gly variant confirmed in trans (0.25 points, VCEP member personal communication), which was previously classified as a variant of unknown significance by the ClinGen LCA/eoRD VCEP (1.25 total points, 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; VCEP member personal communication). At least one proband harboring this variant exhibits a phenotype including a clinical diagnosis of LCA (0.5), absent rod electroretinogram (ERG) responses (0.5), evidence of cone involvement on ERG (1), nystagmus (1), and photophobia (1), optic nerve pallor (0.5), decreased central visual acuity (1) and decreased peripheral vision acuity (1), which together are specific for GUCY2D-related recessive retinopathy (6.5 total points, PMID: 39939324, personal communication from clinician, 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: PM2_Supporting, PP3_Moderate, PM3, PP1, PP4.) (VCEP specifications version 1.0.0).

Met criteria codes

PM2_Supporting ✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 6.205e-7,with 1 allele /1611594 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
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: personal communication from VCEP member (IP).
PP4 ✔	At least one proband harboring this variant exhibits a phenotype including a clinical diagnosis of LCA (0.5), absent rod electroretinogram (ERG) responses (0.5), evidence of cone involvement on ERG (1), nystagmus (1), and photophobia (1), optic nerve pallor (0.5), decreased central visual acuity (1) and decreased peripheral vision acuity (1), which together are specific for GUCY2D-related recessive retinopathy (6.5 total points, PMID: 39939324, personal communication from clinician, PP4).
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: 39939321, My Retina Tracker). This variant has also been reported in at least 1 proband(s) with early-onset severe retinal dystrophy who was compound heterozygous with the c.2660T>G p.Val887Gly variant confirmed in trans (0.25 points, Personal communication from VCEP member (EP)), which was previously classified as a variant of unknown significance by the ClinGen LCA/eoRD VCEP (1.25 total points, PM3).
PP3_Moderate ✔	The computational predictor REVEL gives a score of 0.873, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.774 and predicts a damaging effect on RETGC-1 protein function (PP3_Moderate).

Curation History

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