The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

# *Variant: NM_000180.4(GUCY2D):c.1052A>G (p.Tyr351Cys)*

Version: 1.0

*CA226036*

*98536 (ClinVar)*

**Gene**: GUCY2D (HGNC:3000)
**Condition**: GUCY2D-related recessive retinopathy (MONDO:0100453)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 86ceb82a-6d6d-483c-a8bf-98c684448d1c
**Approved on**: 2025/1/30
**Published on**: 2025/1/30

## *HGVS expressions*

**NM_000180.4(GUCY2D):c.1052A>G (p.Tyr351Cys)**
**NM_000180.4:c.1052A>G**
NC_000017.11:g.8006388A>G
CM000679.2:g.8006388A>G
NC_000017.10:g.7909706A>G
CM000679.1:g.7909706A>G
NC_000017.9:g.7850431A>G
NG_009092.1:g.8719A>G
ENST00000254854.5:c.1052A>G
ENST00000254854.4:c.1052A>G
NM_000180.3:c.1052A>G

**Likely Pathogenic**

**Met criteria codes** 5

PM3_Strong PS3_Supporting PP4_Moderate PM2_Supporting PP3

**Not Met criteria codes** 1

PM6

Evidence Links 1

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.1052A>G (p.Tyr351Cys) variant is predicted to replace the tyrosine at position p.351 with cysteine. This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.000005622, with 9 alleles / 1,600,764 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 0.733, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.644 and predicts a damaging effect on RetGC-1 protein function. 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: 32865313, 15024725). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy**

**who was compound heterozygous with the p.Arg1059Ter variant confirmed in trans (did not count, PMID: 27208204), which has not yet been classified by the ClinGen LCA/eoRD VCEP. It has also been reported in another proband with with early-onset severe retinal dystrophy who was compound heterozygous with the c.2943del variant, classified as pathogenic by the VCEP, confirmed in trans (1 point, PMID: 17525851). (2 total points, PM3_Strong). At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) with an age of onset before age 4 (1 pt). Reported to have nystagmus (1 pt), sluggish pupils (0.5 pts), decreased peripheral vision (1 pt), and decreased central visual acuity (1 pt). ERG and multifocal ERG below normal thresholds (1 pt). Fundoscopy and blue autofluorescence unremarkable. Genetic testing using the ASPER Biotech LCA-Microarray (2006) did not reveal any additional likely variants. (2 pts). Together these are highly specific for GUCY2D-related recessive retinopathy (total 8 points, PMID: 17525851, PP4_Moderate). The protein exhibits a dramatically reduced RD3 signal compared to wild-type control in a GUCY2D pull-down assay. (PS3_Supporting, PMID: 25477517). This variant has been identified as a de novo occurrence in 1 individual with a phenotype specific for GUCY2D-related recessive retinopathy at the PP4_Moderate level (PMID: 17525851). However, the PM6 code was not met since the variant was hypothesized to be on the paternal allele and the genotyping methods were not sufficient to confirm the paternal relationship. 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: PS3_Supporting, PM2_Supporting, PM3_Strong, PP3, and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 01/22/2025).**

**Met criteria codes**

**PM3_Strong** ✔

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: 32865313, 15024725). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Arg1059Ter variant confirmed in trans (did not count, PMID: 27208204), which has not yet been classified by the ClinGen LCA / eoRD VCEP. It has also been reported in another proband with with early-onset severe retinal dystrophy who was compound heterozygous with the c.2943del variant, classified as pathogenic by the VCEP, confirmed in trans (1 point, PMID: 17525851). (2 total points, PM3_Strong).

**PS3_Supporting** ✔

Dramatically reduced RD3 signal comparable to wild-type control in GUCY2D pull-down.

Wild-type RD3 and either wild-type or mutant GUCY2D(GC1) were exogenously expressed in HEK293 cells. Lysates were then immunoprecipitated with anti-RD3 or anti-GC1antibodies and pull-down results were probed on a western blot. Results showed that, compared with WT GC1, the binding efficiency was significantly compromised between RD3 and 10 LCA1 mutants, including Y351C. PubMed:25477517

**PP4_Moderate** ✔

At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) with an age of onset before age 4 (1 pt). Reported to have nystagmus (1 pt), sluggish pupils (0.5 pts), decreased peripheral vision (1 pt), and decreased central visual acuity (1 pt). ERG and multifocal ERG below normal thresholds (1 pt). Fundoscopy and blue autofluorescence unremarkable. Genetic testing using the ASPER Biotech LCA-Microarray (2006) did not reveal any additional likely variants. (2 pts). Together these are highly specific for GUCY2D-related recessive retinopathy (total 8] points, PMID: 17525851, PP4_Moderate).

**PM2_Supporting** ✔

This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000005622, with 9 alleles / 1600764 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).

**PP3** ✔

The computational predictor REVEL gives a score of 0.733, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and predicts a damaging effect on RetGC function.

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM6** | ✖ | This variant has been identified as a de novo occurrence in 1 individual with a phenotype specific for GUCY2D-related recessive retinopathy at the PP4_Moderate level (PMID: 17525851). However, the PM6 code was not met since the variant was hypothesized to be on the paternal allele and the genotyping methods were not sufficient to confirm the paternal relationship. |

## Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.