

Variant: *NM_000180.4(GUCY2D):c.1694T>C (p.Phe565Ser)*

Version: 1.0

CA226054 [↗](#)

9350 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e4081a29-cfa7-40d5-b266-5ca0950eaed2

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HGVS expressions

NM_000180.4:c.1694T>C

NM_000180.4(GUCY2D):c.1694T>C (p.Phe565Ser)

NC_000017.11:g.8009531T>C

CM000679.2:g.8009531T>C

NC_000017.10:g.7912849T>C

CM000679.1:g.7912849T>C

NC_000017.9:g.7853574T>C

NG_009092.1:g.11862T>C

ENST00000254854.5:c.1694T>C

ENST00000254854.4:c.1694T>C

NM_000180.3:c.1694T>C

Pathogenic

Met criteria codes **6**

PP1_Strong

BP2

PM2_Supporting

PS3_Supporting

PM3_Strong

PP4

Not Met criteria codes **1**

PP3

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.1694T>C (p.Phe565Ser) is a missense variant predicted to replace phenylalanine with serine at position p.565. This variant is present in gnomAD v4.1.0 at a total allele frequency of 6.197e-7, with 1 allele / 1613704 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting). This variant has been reported in a homozygous proband with early-onset severe retinal dystrophy in cis with the NM_000180.4(GUCY2D):c.2633_2636del (p.Gln878ArgfsTer17) variant, which has been classified as pathogenic by the ClinGen LCA/eoRD VCEP (VCEP member-provided data, BP2). This variant has also been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 pt, PMID:

8944027), and in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the variant confirmed in trans with the NM_000180.4(GUCY2D):c.2302C>T (p.Arg768Trp) variant (1 pt, PMID: 16505055), which has been classified as pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). Please note that one of these patients has been genotyped in a way that did not rule out the presence or absence of another GUCY2D variant in cis (PMID: 16505055). This proband exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset at 3 months (1 pt), night blindness (0.5 pts), nystagmus (1 pt), and visual acuity limited to light perception (1 pt), which together are specific for GUCYD2-related recessive retinopathy (total 4 pts, PMID: 16505055, PP4). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 3 similarly affected relatives in two different families, with the variant present in the homozygous state (PMID: 8944027, PP1_Strong). The computational predictor REVEL gives a score of 0.494, which is below the ClinGen LCA/eoRD VCEP threshold of ≥ 0.644 and does not predict a damaging effect on RETGC-1 protein function. The variant exhibited inability to be stimulated by GCAP1 (PMID: 9888789), reduced RD3 binding by co-immunoprecipitation (PMID: 25477517), and failure to localize to the plasma membrane along with RD3 and GCAP1 when exogenously expressed (PMID: 25477517), indicating that it triggers a severe defect in protein function (PS3_Supporting). In summary, this variant meets the criteria to be classified as 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, PP1_Strong, PP4, and BP2. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PP1_Strong			The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 3 similarly affected relatives in two different families, with the variant present in the homozygous state (PMID: 8944027, PP1_Strong).
BP2			This variant has been reported in a homozygous proband with early-onset severe retinal dystrophy in cis with the NM_000180.4(GUCY2D):c.2633_2636del (p.Gln878ArgfsTer17) variant, which has been classified as pathogenic by the ClinGen LCA / eoRD VCEP (VCEP member-provided data, BP2). This patient was not included in the PM3 count.
PM2_Supporting			This variant is present in gnomAD v.4.1.0 at a total allele frequency of 6.197e-7, with 1 allele / 1613704 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of < 0.0004 (PM2_Supporting).
PS3_Supporting			The variant (referred to as "F514S") exhibited ~15% enzymatic activity in the absence of GCAP stimulation in a guanylate cyclase assay in COS-1 cells relative to the wild-type control (Fig. 2A), which lacks GCAP stimulation and therefore is not an approved PS3_Supporting assay for the ClinGen LCA / eoRD VCEP. The variant also exhibited inability to be stimulated by GCAP1 (Fig. 3), indicating that it triggers a severe defect in protein function (PMID: 9888789, PS3_Supporting). The variant showed reduced RD3 binding by western blot when co-immunoprecipitated by either anti-GUCY2D or anti-RD3 antibody (PMID: 25477517). When the variant was co-expressed with RD3 and GCAP1 in COS-7 cells, all three proteins failed to reach the plasma membrane (PMID: 25477517).
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 pt, PMID: 8944027). The variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the variant confirmed in trans with the NM_000180.4(GUCY2D):c.2302C>T (p.Arg768Trp) variant (1 pt, PMID: 16505055), which has been classified as pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong). Please note that one of these patients has been genotyped in a way that did not rule out the presence or absence of another GUCY2D variant in cis (PMID: 16505055).
PP4			At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset at 3 months (1 pt), night blindness (0.5 pts), nystagmus (1 pt), and visual acuity limited to light perception (1 pt), which together are specific for GUCYD2-related recessive retinopathy (total 4 pts, PMID: 16505055, PP4).

16505055, PP4). Please note that this patient has been genotyped in a way that did not rule out the presence or absence of another GUCY2D variant in cis.

Not Met criteria codes

PP3

The computational predictor REVEL gives a score of 0.494, which is below the ClinGen LCA / eoRD VCEP threshold of ≥ 0.644 and does not predict a damaging effect on RetGC-1 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.00 for all splicing types, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥ 0.2 and does not strongly predict an impact on splicing.

Curation History

Showing 1 to 1 of 1 rows

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