

Variant: *NM_000180.4(GUCY2D):c.937C>T (p.Arg313Cys)*

Version: 1.0

CA226156 [↗](#)

98611 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: fc66e7d9-7bd4-4c3c-862c-ce8f5a676e18

Approved on: 2025/1/30

Published on: 2025/1/30

HGVS expressions

NM_000180.4:c.937C>T

NM_000180.4(GUCY2D):c.937C>T (p.Arg313Cys)

NC_000017.11:g.8004067C>T

CM000679.2:g.8004067C>T

NC_000017.10:g.7907385C>T

CM000679.1:g.7907385C>T

NC_000017.9:g.7848110C>T

NG_009092.1:g.6398C>T

ENST00000254854.5:c.937C>T

ENST00000254854.4:c.937C>T

NM_000180.3:c.937C>T

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP1

PM3

PM2_Supporting

Not Met criteria codes **3**

PS3

PP3

BS3

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

NM_000180.4(GUCY2D):c.937C>T (p.Arg313Cys) is a missense variant predicted to replace arginine with cysteine at position p.313. This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.000009334, with 15 alleles / 1,607,084 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 at least 2 probands with early-onset severe retinal dystrophy who also harbored either the NM_000180.4(GUCY2D):c.1343C>A (p.Ser448Ter) variant (suspected but not confirmed in trans, PMID:10951519) or the NM_000180.4(GUCY2D):c.3078_3083dup (p.Ile1027_Leu1028dup) variant (confirmed in trans, PMID: 34048777), each which have been previously classified as either pathogenic or likely pathogenic by the

LCA/eoRD VCEP (1.5 total pts,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 compound heterozygous state (VCEP member-provided data, PP1). At least one proband harboring this variant exhibits a phenotype including a diagnosis of Leber congenital amaurosis (0.5 pts) with onset at age 0.3 years (1 pt), genotyping by exome sequencing with no alternative cause of retinal disease identified (4 pts), poor vision with no light perception (1 pt), roving nystagmus (1 pt), attenuated vessels (0.5 pts), and extinguished electroretinogram responses from rods (0.5 pts) and cones (1 pt), which together are highly specific for GUCY2D-related recessive retinopathy (9.5 total points, PMID: 34048777, PP4_Moderate). 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, PM3, PP1, and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PP4_Moderate			At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 points) with age of onset at 0.3 years (1 pt), genotyping by exome sequencing with no alternative cause of retinal disease identified (4 pts), poor vision (1 pt), roving nystagmus (1 pt), no light perception, attenuated vessels (0.5 pts), and extinguished electroretinogram responses from rods (0.5 pts) and cones (1 pt). Together these are specific for GUCY2D-related recessive retinopathy total of 9.5 points, PMID: 34048777, PP4_Moderate).
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 compound heterozygous state (VCEP member-provided data, PP1).
PM3			This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who also harbored either the NM_000180.4(GUCY2D):c.1343C>A (p.Ser448Ter) variant (suspected but not confirmed in trans, PMID:10951519) or the NM_000180.4(GUCY2D):c.3078_3083dup (p.Ile1027_Leu1028dup) variant (confirmed in trans, PMID: 34048777), each which have been previously classified as either pathogenic or likely pathogenic by the LCA / eoRD VCEP (1.5 total pts, PM3).
PM2_Supporting			This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000009334, with 15 alleles / 1,607,084 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).

Not Met criteria codes

PS3			The variant exhibited ~100% enzymatic activity in a guanylate cyclase assay relative to the wild-type control, which is higher than the ClinGen LCA / eoRD VCEP BS3_Supporting threshold of >50% activity, indicating that it does not trigger a severe defect in protein function, however, it lies in the extracellular domain that is considered ineligible for PS3 or BS3 due to incompatibility with in vitro activity assays (PMID: 11328726). PubMed:11328726 
PP3			The computational predictor REVEL gives a score of 0.639, which is below the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and does not predict a damaging effect on GUCY2D function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.0, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
BS3			The variant exhibited ~100% enzymatic activity in a guanylate cyclase assay relative to the wild-type control, which is higher than the ClinGen LCA / eoRD VCEP BS3_Supporting threshold of >50% activity, indicating that it does not trigger a severe defect in protein function. However, the variant lies within the extracellular domain that is considered ineligible for PS3 or BS3 due to incompatibility with in vitro activity assays (PMID: 11328726).

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Curation History [↗](#)

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