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Variant: NM_000180.4(GUCY2D):c.1618C>T (p.Arg540Cys)

Version: 1.0

CA226052

98546 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 90550901-0891-4b5c-ad2a-8f7bc7918612
Approved on: 2025-01-30
Published on: 2025-01-30

HGVS expressions

NM_000180.4:c.1618C>T
NM_000180.4(GUCY2D):c.1618C>T (p.Arg540Cys)
NC_000017.11:g.8007982C>T
CM000679.2:g.8007982C>T
NC_000017.10:g.7911300C>T
CM000679.1:g.7911300C>T
NC_000017.9:g.7852025C>T
NG_009092.1:g.10313C>T
ENST00000254854.5:c.1618C>T
ENST00000254854.4:c.1618C>T
NM_000180.3:c.1618C>T

Uncertain Significance

Met criteria codes 1

PM2_Supporting

Not Met criteria codes 2

PP3 PM3

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.1618C>T (p.Arg540Cys) variant is predicted to replace the arginine at position p.540 with cysteine. This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.00005391, with 87 alleles / 1,613,652 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 0.609, which is below the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and does not predict a damaging effect on RetGC-1 protein function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.02, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. This variant was reported in individual with LCA but

no second variant was identified. It was also seen heterozygously in a patient with a macular dystrophy likely caused by ABCA4 variants (PM3_not met; PMIDs:10951519, 29555955). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for GUCY2D-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM2_Supporting. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.00005391, with 87 alleles / 1,613,652 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.609, 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 0.02, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM3	✖	Reported in individual with LCA but no second variant identified. Also seen heterozygously in a patient with a macular dystrophy likely caused by ABCA4 variants (PMIDs:10951519, 29555955).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000180.4(GUCY2D):c.1618C>T (p....	Uncertain Significance	GUCY2D-Related Recessive Retinopathy	2025-01-30	1.0	ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GUCY2D Version 1.0.0	GUCY2D

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