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Variant: NM_000180.4(GUCY2D):c.2983C>T (p.Arg995Trp)

Version: 1.0

CA226112

98584 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: d029d544-78fc-4d28-ad58-ed27e8507663
Approved on: 2025/1/30
Published on: 2025/1/30

HGVS expressions

NM_000180.4(GUCY2D):c.2983C>T (p.Arg995Trp)
NM_000180.4:c.2983C>T
NC_000017.11:g.8015781C>T
CM000679.2:g.8015781C>T
NC_000017.10:g.7919099C>T
CM000679.1:g.7919099C>T
NC_000017.9:g.7859824C>T
NG_009092.1:g.18112C>T
ENST00000254854.5:c.2983C>T
ENST00000254854.4:c.2983C>T
NM_000180.3:c.2983C>T

Likely Pathogenic

Met criteria codes 5

PM1 PS3_Supporting PP3_Moderate PM2_Supporting PP4

Not Met criteria codes 1

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

NM_000180.4(GUCY2D):c.2983C>T (p.Arg995Trp) is a missense variant that replaces arginine with tryptophan at position p.995, which is located within the active site, a well-characterized functional domain required that binds the GTP substrate and the Mg ion and is required for enzymatic activity (PM1, PMID: 9391039). This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000004342, with 7 alleles / 1,612,258 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 harbored the variant in the compound heterozygous state with either the NM_000180.4:c.2765A>G (p.Tyr922Cys) variant confirmed in trans (PMID: 29844330) or the

NM_000180.4(GUCY2D):c.387C>A (p.Asn129Lys) variant suspected in trans (PMID: 10951519). However, the probands were not counted for PM3 to avoid circularity. At least one proband harboring this variant exhibits a phenotype including clinical diagnosis of Leber congenital amaurosis (0.5 pts) with onset at birth (1 pt), inability to follow light or objects, nystagmus (1 pt), normal fundus at birth, RPE mottling (0.5 pts), non-recordable electroretinogram responses from both rods (0.5 pts) and cones (1 pt), severe hyperopia and severe photophobia (1 pt), non-recordable visual field (1 pt) and congenital blindness (1 pt), which together are specific for GUCY2D-related recessive retinopathy (total 7.5 points, PMID: 10951519, PP4). The computational predictor REVEL gives a score of 0.842 which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 protein function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.02 for splice acceptor gain, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. The mutant protein showed significantly compromised binding to RD3 relative to the wild-type control when exogenously expressed in HEK293 cells and analyzed by co-immunoprecipitation and western blotting (PMID: 25477517). The variant also exhibited 0% enzymatic activity in a guanylate cyclase activity assay relative to the wild-type control, which is lower than the ClinGen LCA/eoRD VCEP PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PMID: 11328726, PS3_Supporting). 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, PM1, PM2_Supporting, PP3_Moderate, and PP4. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PM1	✔	This variant is a missense substitution at Arg995, which is located within the active site, a well-characterized functional domain required that binds the GTP substrate and the Mg ion and is required for enzymatic activity (PM1, PMID: 9391039).
PS3_Supporting	✔	The mutant protein showed significantly compromised binding to RD3 relative to the wild-type control when exogenously expressed in HEK293 cells and analyzed by co-immunoprecipitation and western blotting (PMID: 25477517). The variant also exhibited 0% enzymatic activity in a guanylate cyclase activity assay relative to the wild-type control, which is lower than the ClinGen LCA / eoRD VCEP PS3_Supporting threshold of <10% activity, indicating that it triggers a severe defect in protein function (PMID: 11328726, PS3_Supporting).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.842 which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.02 for splice acceptor gain, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000004342, with 7 alleles / 1,612,258 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including clinical diagnosis of Leber congenital amaurosis (0.5 pts) with onset at birth (1 pt), inability to follow light or objects, nystagmus (1 pt), normal fundus at birth, RPE mottling (0.5 pts), non-recordable electroretinogram responses from both rods (0.5 pts) and cones (1 pt), severe hyperopia and severe photophobia (1 pt), non-recordable visual field (1 pt) and congenital blindness (1 pt), which together are specific for GUCY2D-related recessive retinopathy (total 7.5 points, PMID: 10951519, PP4).

Not Met criteria codes

PM3	✖	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who harbored the variant in the compound heterozygous state with either the NM_000180.4:c.2765A>G (p.Tyr922Cys) variant confirmed in trans (PMID: 29844330) or the NM_000180.4(GUCY2D):c.387C>A (p.Asn129Lys) variant suspected in trans (PMID: 10951519). However, the probands were not counted for PM3 to avoid circularity.

Curation History

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