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Variant: NM_000180.4(GUCY2D):c.1996C>T (p.Arg666Trp)

Version: 1.0

CA8365964

860894 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6fd74226-2024-4f89-b455-5fa657333c4f
Approved on: 2026/9/9
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HGVS expressions

NM_000180.4(GUCY2D):c.1996C>T (p.Arg666Trp)
NM_000180.4:c.1996C>T
NC_000017.11:g.8012489C>T
CM000679.2:g.8012489C>T
NC_000017.10:g.7915807C>T
CM000679.1:g.7915807C>T
NC_000017.9:g.7856532C>T
NG_009092.1:g.14820C>T
ENST00000254854.5:c.1996C>T
ENST00000254854.4:c.1996C>T
NM_000180.3:c.1996C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS3_Supporting PM3 PP4_Moderate

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*
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.1996C>T (p.Arg666Trp) is a missense variant that replaces arginine with tryptophan at amino acid p.666. This variant is present in gnomAD v.4.1.1 at a total allele frequency of 0.00001673, with 27 alleles / 1613832 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 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, PMID: 40478561). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000180.4 (GUCY2D):c.2945del (p.Gly982ValfsTer39) variant suspected in trans (0.5 points, PMID: 29559409), which was previously classified

pathogenic by the ClinGen LCA/eoRD VCEP (1.0 total points, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of congenital stationary night blindness (0.5 pts), vision loss in dim light since early infancy (1 pt), normal retinal structure by optical coherence tomography (1 pt), a non-detectable rod isolating electroretinogram (0.5 pts), evidence of cone involvement on ERG (1 pt) and genotyping by exome sequencing that did not provide an alternative explanation for visual impairment (4 pts), which together are highly specific for GUCY2D-related recessive retinopathy (8 total points, PMID: 29559409, PP4_Moderate). The variant exhibited 0% enzymatic activity in a guanylate cyclase 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 (PS3_Supporting, PMID: 33109612). The computational predictor REVEL gives a score of 0.479, 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 0.04, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. 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, PP4_Moderate, and PS3_Supporting. (VCEP specifications version 1.0.0).

Met criteria codes

PM2_Supporting	✔	This variant is present in gnomAD v.4.1.1 at a total allele frequency of 0.000017, with 27 alleles / 1613832 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
PS3_Supporting	✔	The variant exhibited 0% enzymatic activity in a guanylate cyclase 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 (PS3_Supporting, PMID: 33109612).
PM3	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, PMID: 40478561). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000180.4 (GUCY2D):c.2945del (p.Gly982ValfsTer39) variant suspected in trans (0.5 points, PMID: 29559409), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1.0 total points, PM3).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of congenital stationary night blindness (0.5 pts), vision loss in dim light since early infancy (1 pt), normal retinal structure by optical coherence tomography (1 pt), a non-detectable rod isolating electroretinogram (0.5 pts), evidence of cone involvement on ERG (1 pt) and genotyping by exome sequencing that did not provide an alternative explanation for visual impairment (4 pts), which together are highly specific for GUCY2D-related recessive retinopathy (8 total points, PMID: 29559409, PP4_Moderate).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.479, 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 0.04, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.

Curation History

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