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Variant: NM_000180.4(GUCY2D):c.743C>G (p.Ser248Trp)

Version: 1.0

CA8365564

1445009 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6b75b512-79f7-452a-ae4c-aec715828caf
Approved on: 2025/1/30
Published on: 2025/1/30

HGVS expressions

NM_000180.4:c.743C>G
NM_000180.4(GUCY2D):c.743C>G (p.Ser248Trp)
NC_000017.11:g.8003873C>G
CM000679.2:g.8003873C>G
NC_000017.10:g.7907191C>G
CM000679.1:g.7907191C>G
NC_000017.9:g.7847916C>G
NG_009092.1:g.6204C>G
ENST00000254854.5:c.743C>G
ENST00000254854.4:c.743C>G
NM_000180.3:c.743C>G

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PS3_Supporting PM2_Supporting PP4 PP3_Moderate

Not Met criteria codes 1

PM5

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.743C>G (p.Ser248Trp) is a missense variant predicted to replace serine with tryptophan at position p.248 in the RetGC-1 protein. This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.000001240, with 2 alleles / 1,612,844 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 compound heterozygous with the NM_000180.4(GUCY2D):c.3224+1G>C variant suspected in trans (0.5 points, PMID: 23035049), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (0.5 total points, PM3_Supporting). At least one proband harboring this variant exhibits a phenotype

including diagnosis of Leber congenital amaurosis (0.5 pts), decreased central visual acuity (1 pt) with onset in the first year of life (1 pt), nystagmus (1 pt), decreased peripheral vision (1 pt), retinal vessel attenuation with granularity of peripheral fundus (0.5 pts), outer nuclear layer thickness on OCT within normal limits (1 pt), poor pupillary light response (0.5 pts), and undetectable electroretinogram responses from rods (0.5 pts). and cones (1 pt), which together are highly specific for GUCY2D-related recessive retinopathy (total 8 points, PMID: 23035049, PP4). The computational predictor REVEL gives a score of 0.878, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 protein function (PP3_Moderate). Gucy2e-knockout mouse retinas injected with an adeno-associated virus-packaged GUCY2D construct encoding the p.Ser248Trp variant showed mRNA levels similar to the wild-type control but dramatically reduced protein levels and essentially no cGMP production, indicating that it triggers a severe defect in protein function (PMID: 27881908, PS3_Supporting). Another missense variant in the same codon (NM_000180.4(GUCY2D):c.743C>T (p.Ser248Leu)) has been reported in association with GUCY2D-related recessive retinopathy (PMID: 26957854). However, the variant has not yet been classified by the LCA/eoRD VCEP, so the PM5 code is not met. 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, PP3_Moderate, PM3_Supporting, PP4, and PS3_Supporting. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PM3_Supporting ✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_000180.4(GUCY2D):c.3224+1G>C variant suspected in trans (0.5 points, PMID: 23035049, PMID: 23847139), which was previously classified pathogenic by the ClinGen LCA / eoRD VCEP (0.5 total points, PM3_Supporting).
PS3_Supporting ✔	Gucy2e-knockout mouse retinas injected with an adeno-associated virus-packaged GUCY2D construct encoding the p.Ser248Trp variant showed mRNA levels similar to the wild-type control (Figure 3C) but dramatically reduced protein levels (Figure 3B, Figure 4) and essentially no cGMP production (Figure 3A), indicating that it triggers a severe defect in protein function (PMID: 27881908, PS3_Supporting). The variant exhibited ~125% enzymatic activity in a guanylate cyclase assay relative to the wild-type control, which is higher than the ClinGen LCA / eoRD BS3_Supporting threshold of ≥50% activity, indicating that it preserves normal protein function (PMID: 23035049, Figures 5B and 5D). However, this variant falls within the extracellular domain (occurring between amino acids 52-462), in which variants are known to show no damaging effect in these assays.
PM2_Supporting ✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000001240, with 2 alleles / 1,612,844 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 diagnosis of Leber congenital amaurosis (0.5 pts), decreased central visual acuity (1 pt) with onset in the first year of life (1 pt), nystagmus (1 pt), decreased peripheral vision (1 pt), retinal vessel attenuation with granularity of peripheral fundus (0.5 pts), outer nuclear layer thickness on OCT within normal limits (1 pt), poor pupillary light response (0.5 pts), and undetectable electroretinogram responses from rods (0.5 pts). and cones (1 pt), which together are highly specific for GUCY2D-related recessive retinopathy (total 8 points but no specific criteria, PMID: 23035049, PP4).
PP3_Moderate ✔	The computational predictor REVEL gives a score of 0.878, 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 delta score of 0.06 for acceptor loss, which is below the ClinGen LCA / eoRD VCEP recommended threshold of <0.1 and does not predict an impact on splicing.

Not Met criteria codes

PM5		✖	Another missense variant in the same codon (NM_000180.4(GUCY2D):c.743C>T (p.Ser248Leu)) has been reported in association with GUCY2D-related recessive retinopathy by the ClinGen LCA / eoRD VCEP (PMID: 26957854). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants. However, the variant has not yet been classified by the LCA / eoRD VCEP, so the PM5 code is not met.

Curation History

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