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Variant: NM_000180.4(GUCY2D):c.2302C>T (p.Arg768Trp)

Version: 1.0

CA226075

98563 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7d43eb10-7e4d-44c3-bdb4-81e318efbc44
Approved on: 2025/1/30
Published on: 2025/1/30

HGVS expressions

NM_000180.4(GUCY2D):c.2302C>T (p.Arg768Trp)
NM_000180.4:c.2302C>T
NC_000017.11:g.8013918C>T
CM000679.2:g.8013918C>T
NC_000017.10:g.7917236C>T
CM000679.1:g.7917236C>T
NC_000017.9:g.7857961C>T
NG_009092.1:g.16249C>T
ENST00000254854.5:c.2302C>T
ENST00000254854.4:c.2302C>T
NM_000180.3:c.2302C>T

Pathogenic

Met criteria codes 6

PM3_Strong | PS3_Supporting | PP3_Moderate | PM2_Supporting | PP1 | PP4

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.2302C>T is a missense variant predicted to replace arginine with tryptophan at position p.768. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.0002728, with 440 alleles / 1,612,990 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 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMID: 23035049) and in at least 6 probands with early-onset severe retinal dystrophy who were compound heterozygous, including 2 with either the NM_000180.4(GUCY2D):c.2516del (p.Thr839fs) or NM_000180.4(GUCY2D):c.1633C>T (p.Gln545Ter) variants suspected in trans (1 point,

PMID: 23035049, PMID: 16505055), both of which have been previously classified as pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset at 3 months (1 pt), night blindness (0.5 pts), nystagmus (1 pt), and visual acuity limited to light perception (1 pt), which together are specific for GUCYD2-related recessive retinopathy (total 4 pts, PMID: 16505055, PP4). 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 (PMID: 23035049, PP1). The computational predictor REVEL gives a score of 0.817, which is above the ClinGen LCA/eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on GUCY2D function (PP3_Moderate). The splicing impact predictor SpliceAI gives scores of 0.16 for donor loss and 0.15 for acceptor loss, which are below the ClinGen LCA/eoRD VCEP recommended threshold of 0.2 and do not strongly predict an impact on splicing. The variant exhibited ~0% enzymatic activity when co-expressed with GCAP1 or GCAP2 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 (PMID: 23035049, PMID: 33997691). The variant when co-expressed with GCAP1 and RD3 exhibited dispersal of GCAP1 and RD3 throughout the cell rather than proper localization to the plasma membrane, indicating failure of the variant to interact with either factor (PMID: 33109612). The variant also showed reduced RD3 binding by western blot when co-immunoprecipitated by either anti-GUCY2D or anti-RD3 antibody (PMID: 25477517, PS3_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for GUCY2D-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PS3_Supporting, PM2_Supporting, PM3_Strong, PP1, PP3_Moderate, and PP4. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PM3_Strong	✔	This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMID: 23035049) and in at least 6 probands with early-onset severe retinal dystrophy who were compound heterozygous, including 2 with either the NM_000180.4(GUCY2D):c.2516del (p.Thr839fs) or NM_000180.4(GUCY2D):c.1633C>T (p.Gln545Ter) variants suspected in trans (1 point, PMID: 23035049, PMID: 16505055), both of which have been previously classified as pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong).
PS3_Supporting	✔	The variant exhibited ~0% enzymatic activity when co-expressed with GCAP1 or GCAP2 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 (PMID: 23035049, PMID: 33997691). The variant when co-expressed with GCAP1 and RD3 exhibited dispersal of GCAP1 (Figures 2 and 3) and RD3 (Figures 4 and 5) throughout the cell rather than proper localization to the plasma membrane, indicating failure of the variant to interact with either factor (PMID: 33109612). The variant also showed reduced RD3 binding by western blot when co-immunoprecipitated by either anti-GUCY2D or anti-RD3 antibody (PMID: 25477517, PS3_Supporting).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.817, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on GUCY2D function (PP3_Moderate). The splicing impact predictor SpliceAI gives scores of 0.16 for donor loss and 0.15 for acceptor loss, which are below the ClinGen LCA / eoRD VCEP recommended threshold of 0.2 and do 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 0.0002728, with 440 alleles / 1,612,990 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
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 (PMID: 23035049, PP1).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset at 3 months (1 pt), night blindness (0.5 pts), nystagmus (1 pt), and visual acuity limited to light

perception (1 pt), which together are specific for GUCYD2-related recessive retinopathy (total 4 pts, PMID: 16505055, PP4).

Curation History

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