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Variant: NM_000180.4(GUCY2D):c.1762C>T (p.Arg588Trp)

Version: 1.0

CA287530833

2137915 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 49a53574-6ee6-4d55-8b5d-ce1a2349bbc2
Approved on: 2025-01-30
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HGVS expressions

NM_000180.4:c.1762C>T
NM_000180.4(GUCY2D):c.1762C>T (p.Arg588Trp)
NC_000017.11:g.8012156C>T
CM000679.2:g.8012156C>T
NC_000017.10:g.7915474C>T
CM000679.1:g.7915474C>T
NC_000017.9:g.7856199C>T
NG_009092.1:g.14487C>T
ENST00000254854.5:c.1762C>T
ENST00000254854.4:c.1762C>T
NM_000180.3:c.1762C>T

Pathogenic

Met criteria codes 5

PP1_Strong PP4_Moderate PS3_Supporting PM2_Supporting PM3_Strong

Not Met criteria codes 1

PP3

Evidence Links 1

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.1762C>T (p.Arg588Trp) variant is predicted to replace the arginine at position p.588 with tryptophan. The variant protein exhibited <1.5% of wild-type activity when stimulated with GCAP1, GCAP2, or GCAP3, 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. In addition, the variant protein failed to co-localize with GCAP1 when co-expressed in HEK293 cells (PS3_Supporting, PMID: 36274938). The computational predictor REVEL gives a score of 0.592, which is below the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and does not predict a damaging effect on RetGC-1 protein function. The splicing impact predictor SpliceAI gives a score of 0.2 for an acceptor site gain, which meets the

ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing, however, this variant has been curated based on protein function rather than spliceogenicity, so the PP3 code has not been considered. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000008678, with 14 alleles / 1,613,262 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, PMIDs: 29068479, 37327959). This variant has also been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000180.4(GUCY2D):c.2516del (p.Thr839ArgfsTer27) or the NM_000180.4(GUCY2D):c.307G>A (p.Glu103Lys) variant suspected but not confirmed in trans (PMID: 36274938, VCEP member-provided data), which have been previously classified as either pathogenic or likely pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state, and through a second proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PMID:37327959, VCEP member-provided data, PP1_Strong). At least one proband harboring this variant exhibits a phenotype including diagnosis of early onset retinitis pigmentosa (0.5 pts) with onset in infancy (1 pt), genotyping by an LCA gene panel with no additional likely pathogenic findings (2 pts), electroretinogram showing altered responses from both cones and rods (1.5 pts), dyschromatopsia (1 pt), visual field loss (1 pt), attenuated blood vessels with peripheral pigment (0.5 pts), and night blindness (0.5 pts), which together are specific for GUCY2D-related recessive retinopathy (total 8 points, PMID: 37327959, PP4_moderate). 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_Strong, and PP4. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PP1_Strong	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state, and through a second proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PMID:37327959, VCEP member-provided data, PP1_Strong).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of early onset retinitis pigmentosa (0.5 pts) with onset in infancy (1 pt), genotyping by an LCA gene panel with no additional likely pathogenic findings (2 pts), electroretinogram showing altered responses from both cones and rods (1.5 pts), dyschromatopsia (1 pt), visual field loss (1 pt), attenuated blood vessels with peripheral pigment (0.5 pts), and night blindness (0.5 pts), which together are specific for GUCY2D-related recessive retinopathy (total 8 points, PMID: 37327959, PP4_moderate).
PS3_Supporting	✔	The variant exhibited <1.5% of wt activity when stimulated with GCAP1, GCAP2, or GCAP3. 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 . In addition, variant protein failed to co-localize with GCAP1 when co-expressed in HEK293 cells (PS3_Supporting, PMID: 36274938). The variant exhibited <1.5% of wt activity when stimulated with GCAP1, GCAP2, or GCAP3. 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 . In addition, variant protein failed to co-localize with GCAP1 when co-expressed in HEK293 cells (PS3_Supporting). PubMed:36274938
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000008678, with 14 alleles / 1,613,262 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
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, PMIDs: 29068479, 37327959). This variant has also been reported in at least 2

probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000180.4(GUCY2D):c.2516del (p.Thr839ArgfsTer27) or the NM_000180.4(GUCY2D):c.307G>A (p.Glu103Lys) variant suspected but not confirmed in trans (PMID: 36274938, VCEP member-provided data), which have been previously classified as either pathogenic or likely pathogenic by the ClinGen LCA / eoRD VCEP (2 total points, PM3_Strong).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.592, which is below the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and does not predict a damaging effect on GUCY2D function. PP3 is not met. The splicing impact predictor SpliceAI gives a score of 0.2 for an acceptor site gain, which meets the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing. However, we are curating this based on protein function, not spliceogenicity, so the SpliceAI score is not being considered.

Curation History

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