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Variant: NM_000180.4(GUCY2D):c.307G>A (p.Glu103Lys)

Version: 1.0

CA226122

98590 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: fc5056f3-86f2-497e-a21d-16e5e8850843
Approved on: 2025-01-30
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HGVS expressions

NM_000180.4:c.307G>A
NM_000180.4(GUCY2D):c.307G>A (p.Glu103Lys)
NC_000017.11:g.8003354G>A
CM000679.2:g.8003354G>A
NC_000017.10:g.7906672G>A
CM000679.1:g.7906672G>A
NC_000017.9:g.7847397G>A
NG_009092.1:g.5685G>A
ENST00000254854.5:c.307G>A
ENST00000254854.4:c.307G>A
NM_000180.3:c.307G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM3_Strong PP1 PP4

Not Met criteria codes 2

PP3 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.307G>A (p.Glu103Lys) is a missense variant that is predicted to replace glutamic acid with lysine at position p.103. Another missense variant in the same codon, NM_000180.4(GUCY2D):c.308A>T (p.Glu103Val), has been reported in association with GUCY2D-related recessive retinopathy (PMID: 21602930), and splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants. However, this second variant has not yet been classified by the ClinGen LCA / eoRD VCEP, so PM5 is not met. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.0001749, with 257 alleles / 1,469,548 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 apparently unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000180.4(GUCY2D):c.2595del (p.Lys866fs) variant or the NM_000180.4(GUCY2D):c.91dup (p.Arg31fs) variant confirmed in trans, which were previously classified pathogenic by the ClinGen LCA/eoRD VCEP (2 points, PMID: 29178642, PM3_Strong). 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: 31704230, PP1). At least one proband harboring this variant exhibits a phenotype including diagnosis of LCA (0.5 pts), nystagmus (1 pt), visual acuity limited to light perception (1 pt) since birth (1 pt), flat ERG responses from both rods (0.5 pts) and cones (1 pt), high hypermetropia, being drawn to bright light, sluggish pupillary responses (0.5 pts), eye poking, and normal appearing fundus with some abnormality in the reflection from the inner limiting membrane at high magnification, which together are specific for GUCY2D-related recessive retinopathy (total 5.5 points, PMID: 29178642, PP4). The computational predictor REVEL gives a score of 0.547, 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 0.00, 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_Strong, PP1 and PP4. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.0001749, with 257 alleles / 1,469,548 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 apparently unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_000180.4(GUCY2D):c.2595del (p.Lys866fs) variant or the NM_000180.4(GUCY2D):c.91dup (p.Arg31fs) variant confirmed in trans, which were previously classified pathogenic by the ClinGen LCA / eoRD VCEP (2 points, PMID: 29178642, PM3_Strong).
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: 31704230, PP1).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset before age 5 (1 pt), nystagmus (1), photophobia (1 pt), reduced visual acuity (1 pt), undetectable light-adapted ERG responses (1 pt), reduced or undetectable dark-adapted ERG responses (0.5 pts), and central retinal pigment epithelium atrophy (0.5 pts), which together are specific for GUCY2D-related recessive retinopathy (total 6.5 points, PMID: 31704230, PP4).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.547, which is below the ClinGen LCA / eoRD VCEP threshold of ≥0.644 and does not predict a damaging effect on RetGC-1 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.00, which is below the ClinGen LCA / eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM5	✖	Another missense variant in the same codon (NM_000180.4(GUCY2D):c.308A>T (p.Glu103Val)) has been reported in association with GUCY2D-related recessive retinopathy (PMID: 21602930), and splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants. However, this second variant has not yet been classified by the ClinGen LCA / eoRD VCEP, so PM5 is not met.

Curation History

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