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Variant: NM_000180.4(GUCY2D):c.935C>T (p.Thr312Met)

Version: 1.0

CA226155

98610 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3d9ba5ca-91d0-4d68-b098-37e9f4237e2d
Approved on: 2025/1/30
Published on: 2025/1/30

HGVS expressions

NM_000180.4(GUCY2D):c.935C>T (p.Thr312Met)
NM_000180.4:c.935C>T
NC_000017.11:g.8004065C>T
CM000679.2:g.8004065C>T
NC_000017.10:g.7907383C>T
CM000679.1:g.7907383C>T
NC_000017.9:g.7848108C>T
NG_009092.1:g.6396C>T
ENST00000254854.5:c.935C>T
ENST00000254854.4:c.935C>T
NM_000180.3:c.935C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM3 PP4 PP3_Moderate

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

The NM_000180.4(GUCY2D):c.935C>T (p.Thr312Met) variant is predicted to replace the threonine at position p.312 with methionine. This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000005599, with 9 alleles / 1,607,292 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting). The computational predictor REVEL gives a score of 0.794, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 protein function (PP3_Moderate). This variant has been reported in at least 5 unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous for the variant. The patient reported in PMID #19959640 has the p.Arg795Trp variant, unclassified by the

LCA/eoRD VCEP, suspected in trans (not counted). The patient reported in PMID #26047050 has the p.Arg332Pro variant, currently unclassified, confirmed in trans (0.25 pts). The 2 unrelated patients reported in PMIDs #27375279 and #27422788 both have the p.Leu251Pro variant, currently unclassified, confirmed in trans (0.5 pts). The patient reported in PMID #27375279 has the p.Ser1007Leu variant, currently unclassified, confirmed in trans (0.25 points) (1 total point, PM3). At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) before age 1 (1 pt), nystagmus (1 pt), poor vision (1 pt), extinguished rod and cone ERGs (1.5 pts), attenuated vessels (0.5 pts) and no foveal reflex which together are specific for GUCY2D-related recessive retinopathy (total 5.5 points, PMID: 21602930, PP4). 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, PP4, PM3. (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 0.000005599, with 9 alleles / 1,607,292 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
PM3	✔	This variant has been reported in at least 5 unrelated probands with early-onset severe retinal dystrophy who were compound heterozygous for the variant. The patient reported in PMID #19959640 has the p.Arg795Trp variant, unclassified by the LCA/eoRD VCEP, suspected in trans (not counted). The patient reported in PMID #26047050 has the p.Arg332Pro variant, currently unclassified, confirmed in trans (0.25 pts). The 2 unrelated patients reported in PMIDs #27375279 and #27422788 both have the p.Leu251Pro variant, currently unclassified, confirmed in trans (0.5 pts). The patient reported in PMID #27375279 has the p.Ser1007Leu variant, currently unclassified, confirmed in trans (0.25 points) (1 total point, PM3).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts) before age 1 (1 pt), nystagmus (1 pt), poor vision (1 pt), extinguished rod and cone ERGs (1.5 pts), attenuated vessels (0.5 pts) and no foveal reflex, which together are specific for GUCY2D-related recessive retinopathy (total 5.5 points, PMID: 21602930, PP4).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.794, which is above the ClinGen LCA / eoRD VCEP threshold of ≥0.773 and predicts a damaging effect on RetGC-1 function (PP3_Moderate).

Curation History

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