

Variant: NM_000180.4:c.3020C>A

Version: 1.0

CA397955377 [↗](#)

Gene: GUCY2D ([HGNC:3000](#))

Condition: GUCY2D-related recessive retinopathy ([MONDO:0100453](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: ced8a8d3-e681-484a-a99e-c962e047c599

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HGVS expressions

NM_000180.4:c.3020C>A

NC_000017.11:g.8015818C>A

CM000679.2:g.8015818C>A

NC_000017.10:g.7919136C>A

CM000679.1:g.7919136C>A

NC_000017.9:g.7859861C>A

NG_009092.1:g.18149C>A

ENST00000254854.5:c.3020C>A

ENST00000254854.4:c.3020C>A

NM_000180.3:c.3020C>A

Likely Pathogenic

Met criteria codes **2**

PM2_Supporting

PVS1

Not Met criteria codes **2**

PP4

PM3

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.3020C>A (p.Ser1007Ter) is a nonsense variant that introduces a premature stop codon into exon 18 of 20 and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1). This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.0000006202, with 1 allele / 1,612,284 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.982G>C (p.Ala328Pro) variant confirmed in trans (VCEP member-provided data) but has not been counted for PM3 to avoid circularity. The proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with genotyping by next-generation sequencing

panel that did not identify an alternative basis for disease (2 pts), which are not sufficiently specific for GUCY2D-related recessive retinopathy to meet the PP4 code (total 2.5 points, VCEP member-provided data). In summary, this variant meets the criteria to be classified as a Likely Pathogenic for GUCY2D-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PVS1 and PM2_Supporting. (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 0.0000006202, with 1 allele / 1,612,284 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
PVS1			This is a nonsense variant that introduces a premature stop codon into exon 18 of 20 and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1).

Not Met criteria codes

PP4			At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with genotyping by next-generation sequencing panel that did not identify an alternative basis for disease (2 pts), which are not sufficiently specific for GUCY2D-related recessive retinopathy to meet the PP4 code (total 2.5 points, VCEP member-provided data).
PM3			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.982G>C (p.Ala328Pro) variant confirmed in trans (VCEP member-provided data) but has not been counted for PM3 to avoid circularity.

Curation History

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