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Variant: NM_000180.4(GUCY2D):c.1343C>A (p.Ser448Ter)

Version: 1.0

CA226043

98540 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 36b13eab-bc25-4d08-8044-bd6407e0e7e8
Approved on: 2025/1/31
Published on: 2025/1/31

HGVS expressions

NM_000180.4(GUCY2D):c.1343C>A (p.Ser448Ter)
NM_000180.4:c.1343C>A
NC_000017.11:g.8006679C>A
CM000679.2:g.8006679C>A
NC_000017.10:g.7909997C>A
CM000679.1:g.7909997C>A
NC_000017.9:g.7850722C>A
NG_009092.1:g.9010C>A
ENST00000254854.5:c.1343C>A
ENST00000254854.4:c.1343C>A
NM_000180.3:c.1343C>A

Pathogenic

Met criteria codes 3

PVS1 | PM2_Supporting | 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.1343C>A (p.Ser448Ter) is a nonsense variant that introduces a premature stop codon into exon 4 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 0.00001242, with 20 alleles / 1610586 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) during the first year of life (1 pt), as well as nystagmus (1 pt), non-recordable electroretinogram responses from both rods (0.5 pts) and cones (1 pt), and normal fundus, which together are specific for

GUCY2D-related recessive retinopathy (total 4 points, PMID: 10951519, PP4). 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: PVS1, PM2_Supporting, and PP4. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PVS1	✔	This is a nonsense variant that introduces a premature stop codon into exon 4 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).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.00001242, with 20 alleles / 1610586 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) during the first year of life (1 pt), as well as nystagmus (1 pt), non-recordable electroretinogram responses from both rods (0.5 pts) and cones (1 pt), and normal fundus, which together are specific for GUCY2D-related recessive retinopathy (total 4 points, PMID: 10951519, PP4).

Curation History

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