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Variant: NM_000180.4(GUCY2D):c.1633C>T (p.Gln545Ter)

Version: 1.0

CA397949792

689384 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 708e50c7-c859-4f52-8aff-612bdbb2b055
Approved on: 2025/1/31
Published on: 2025/1/31

HGVS expressions

NM_000180.4(GUCY2D):c.1633C>T (p.Gln545Ter)
NM_000180.4:c.1633C>T
NC_000017.11:g.8007997C>T
CM000679.2:g.8007997C>T
NC_000017.10:g.7911315C>T
CM000679.1:g.7911315C>T
NC_000017.9:g.7852040C>T
NG_009092.1:g.10328C>T
ENST00000254854.5:c.1633C>T
ENST00000254854.4:c.1633C>T
NM_000180.3:c.1633C>T

Pathogenic

Met criteria codes 3

PM2_Supporting PP4 PVS1

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.1633C>T (p.Gln545Ter) is a nonsense variant that introduces a premature stop codon into exon 7 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 0.000002479, with 4 alleles /1613362 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), nystagmus (1 pt), visual impairment (1 pt) noted in the first year of life (1 pt), nondetectable ERG responses from rods (0.5 pts) and cones (1 pt), and high hypermetropia, which together are specific for

GUCY2D-related recessive retinopathy (5 pts total, PMID: 29178642, 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

PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000002479, with 4 alleles /1613362 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), nystagmus (1 pt), visual impairment (1 pt) noted in the first year of life (1 pt), nondetectable ERG responses from rods (0.5 pts) and cones (1 pt), and high hypermetropia, which together are specific for GUCY2D-related recessive retinopathy (5 pts total, PMID: 29178642, PP4).
PVS1	✔	This is a nonsense variant that introduces a premature stop codon into exon 7 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).

Curation History

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