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Variant: NM_000180.4(GUCY2D):c.1245del (p.Phe415fs)

Version: 1.0

CA915949552

803313 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: 53cb3135-d743-49c8-bb7f-db0b047108e7
Approved on: 2025/1/30
Published on: 2025/1/30

HGVS expressions

NM_000180.4:c.1245del
NM_000180.4(GUCY2D):c.1245del (p.Phe415fs)
NC_000017.11:g.8006581del
CM000679.2:g.8006581del
NC_000017.10:g.7909899del
CM000679.1:g.7909899del
NC_000017.9:g.7850624del
NG_009092.1:g.8912del
ENST00000254854.5:c.1245del
ENST00000254854.4:c.1245del
NM_000180.3:c.1245del

Pathogenic

Met criteria codes 4

PVS1 PM2_Supporting PP1 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.1245del (p.Phe415Leufs*73) is a loss of function variant in which the deletion of a T at c.1245 in exon 4 of 20 causes a frameshift and early termination 73 codons after p.Phe415. This premature stop codon 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 absent from gnomAD v. 4.1.0 (PM2_Supporting). The variant has been reported to segregate with LCA through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 32865313). The patient's phenotype or family history is highly specific for the gene, with at least one proband harboring this variant exhibiting a phenotype including a diagnosis of LCA / eoRD (0.5pts), previous

genetic testing that did not provide an alternative explanation for visual impairment (2 pts), symptomatic onset between birth and 5 years (1 pt), nystagmus (1 pt), decreased peripheral vision (1 pt), and decreased central vision (1 pt) which together are specific for GUCY2D-related recessive retinopathy (6.5 total points, PMID: 32865313, 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, PP1, and PP4. (VCEP specifications version 1.0.0; date of approval 01/22/2025).

Met criteria codes

PVS1	✔	This is a frameshift 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 absent from gnomAD v. 4.1.0 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with LCA through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PP1; PMID: 32865313).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA/eoRD (0.5pts), previous genetic testing that did not provide an alternative explanation for visual impairment (2 pts), symptomatic onset between birth and 5 years (1 pt), nystagmus (1 pt), decreased peripheral vision (1 pt), and decreased central vision (1 pt) which together are specific for GUCY2D-related recessive retinopathy (6.5 total points, PMID: 32865313, PP4).

Curation History

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