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Variant: NM_000180.4(GUCY2D):c.3224+1G>C

Version: 1.0

CA8366346

581095 (ClinVar)

Gene: GUCY2D (HGNC:3000)
Condition: GUCY2D-related recessive retinopathy (MONDO:0100453)
Inheritance Mode: Autosomal recessive inheritance
UUID: ab8e78d3-4956-4737-b2ae-ae29592ee690
Approved on: 2025-01-31
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HGVS expressions

NM_000180.4:c.3224+1G>C
NM_000180.4(GUCY2D):c.3224+1G>C
NC_000017.11:g.8016291G>C
CM000679.2:g.8016291G>C
NC_000017.10:g.7919609G>C
CM000679.1:g.7919609G>C
NC_000017.9:g.7860334G>C
NG_009092.1:g.18622G>C
ENST00000254854.5:c.3224+1G>C
ENST00000254854.4:c.3224+1G>C
ENST00000574510.1:n.162+1G>C
NM_000180.3:c.3224+1G>C

Pathogenic

Met criteria codes 3

PP4 PM2_Supporting 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.3224+1G>C disrupts a canonical splice site in intron 18 and is predicted to lead to skipping of an out-of-frame exon and disruption of a critical C-terminal region of GUCY2D (PVS1). This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000005125, with 8 alleles /1561036 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), decreased central visual acuity (1 pt) with onset in the first year of life (1 pt), nystagmus (1 pt), decreased peripheral

vision (1 pt), retinal vessel attenuation with granularity of peripheral fundus (0.5 pts), outer nuclear layer thickness on OCT within normal limits (1 pt), poor pupillary light response (0.5 pts), and undetectable electroretinogram responses from rods (0.5 pts). and cones (1 pt), which together are highly specific for GUCY2D-related recessive retinopathy but cannot reach the PP4_Moderate level without genetic testing details (total 8 points, PMID: 23035049, 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

PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), decreased central visual acuity (1 pt) with onset in the first year of life (1 pt), nystagmus (1 pt), decreased peripheral vision (1 pt), retinal vessel attenuation with granularity of peripheral fundus (0.5 pts), outer nuclear layer thickness on OCT within normal limits (1 pt), poor pupillary light response (0.5 pts), and undetectable electroretinogram responses from rods (0.5 pts). and cones (1 pt), which together are highly specific for GUCY2D-related recessive retinopathy (total 8 points, PMID: 23035049) Insufficient details about genetic testing prevent PP4_moderate from being met so only PP4 is met.
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.000005125, with 8 alleles /1561036 total alleles, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0004 (PM2_Supporting).
PVS1	✔	This variant disrupts a canonical splice site in intron 18 and is predicted to lead to skipping of an out-of-frame exon and disruption of a critical C-terminal region of GUCY2D (PVS1).

Curation History

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