The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_033508.3:c.623C>G

Version: 1.0

CA367401307

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: cd129ccc-1ba0-4fe9-99f1-ccf49b2841aa
Approved on: 2026/1/28
Published on: 2026/1/28

HGVS expressions

NM_033508.3:c.623C>G
NC_000007.14:g.44149813G>C
CM000669.2:g.44149813G>C
NC_000007.13:g.44189412G>C
CM000669.1:g.44189412G>C
NC_000007.12:g.44155937G>C
NG_008847.1:g.44611C>G
NG_008847.2:g.53358C>G
ENST00000395796.8:c.*624C>G
ENST00000616242.5:c.626C>G
ENST00000682635.1:n.1112C>G
ENST00000345378.7:c.629C>G
ENST00000403799.8:c.626C>G
ENST00000671824.1:c.626C>G
ENST00000673284.1:c.626C>G
ENST00000345378.6:c.629C>G
ENST00000395796.7:c.623C>G
ENST00000403799.7:c.626C>G
ENST00000437084.1:c.575C>G
ENST00000616242.4:c.623C>G
NM_000162.3:c.626C>G
NM_033507.1:c.629C>G
NM_033508.1:c.623C>G
NM_000162.4:c.626C>G
NM_001354800.1:c.626C>G
NM_033507.2:c.629C>G
NM_033508.2:c.623C>G
NM_000162.5:c.626C>G
NM_033507.3:c.629C>G

Likely Pathogenic

Met criteria codes 6

PM2_Supporting PP2 PP3 PS4_Moderate PP4_Moderate PM5_Supporting

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.626C>G variant in the glucokinase gene, GCK, causes an amino acid change of threonine to arginine at codon 209 (p.(Thr209Arg)) of NM_000162.5. GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2). This variant is absent from gnomAD v4.1 (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.982, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 22035297, 35592779, internal lab contributors). Additionally, one of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative autoantibodies) (PP4_Moderate; PMID: 35592779). Another missense variant at the same residue, c.626C>T (p.Thr209Met), has been classified as pathogenic by the ClinGen MDEP; however, p.Thr209Arg has a smaller Grantham distance (PM5_Supporting). In summary, c.626C>G meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4_Moderate, PP4_Moderate, PM2_Supporting, PM5_Supporting, PP2, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP2	✔	GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.982, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4_Moderate	✔	This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 22035297, 35592779, internal lab contributors).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative autoantibodies) (PP4_Moderate; PMID: 35592779).
PM5_Supporting	✔	Another missense variant at the same residue, c.626C>T (p.Thr209Met), has been classified as pathogenic by the ClinGen MDEP; however, p.Thr209Arg has a smaller Grantham distance (PM5_Supporting).

Curation History

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