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.622A>G

Version: 1.0

CA367401315

3661587 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e9123f2f-37e0-4a94-ab25-817aadd318e0
Approved on: 2026/1/28
Published on: 2026/1/28

HGVS expressions

NM_033508.3:c.622A>G
NC_000007.14:g.44149814T>C
CM000669.2:g.44149814T>C
NC_000007.13:g.44189413T>C
CM000669.1:g.44189413T>C
NC_000007.12:g.44155938T>C
NG_008847.1:g.44610A>G
NG_008847.2:g.53357A>G
ENST00000395796.8:c.*623A>G
ENST00000616242.5:c.625A>G
ENST00000682635.1:n.1111A>G
ENST00000345378.7:c.628A>G
ENST00000403799.8:c.625A>G
ENST00000671824.1:c.625A>G
ENST00000673284.1:c.625A>G
ENST00000345378.6:c.628A>G
ENST00000395796.7:c.622A>G
ENST00000403799.7:c.625A>G
ENST00000437084.1:c.574A>G
ENST00000616242.4:c.622A>G
NM_000162.3:c.625A>G
NM_033507.1:c.628A>G
NM_033508.1:c.622A>G
NM_000162.4:c.625A>G
NM_001354800.1:c.625A>G
NM_033507.2:c.628A>G
NM_033508.2:c.622A>G
NM_000162.5:c.625A>G
NM_033507.3:c.628A>G

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PM1

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.625A>G variant in the glucokinase gene, GCK, causes an amino acid change of threonine to alanine at codon 209 (p.(Thr209Ala)) 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 0.958, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and persistent mild hyperglycemia) (PP4_Moderate; internal lab contributors). Another missense variant at the same residue, c.626C>T (p.Thr209Met), has been classified as pathogenic by the ClinGen MDEP; however, p.Thr209Ala has a smaller Grantham distance (PM5_Supporting). In summary, c.625A>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): PP4_Moderate, PM2_Supporting, PM5_Supporting, PP2, PP3.

Met criteria codes

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 0.958, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and persistent mild hyperglycemia) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
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.Thr209Ala has a smaller Grantham distance (PM5_Supporting).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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