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.587T>A

Version: 1.1

CA367401432

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: a8e567b8-2caf-43b3-8cbf-0fccee5c9de0
Approved on: 2025/11/26
Published on: 2025/11/26

HGVS expressions

NM_033508.3:c.587T>A
NC_000007.14:g.44149849A>T
CM000669.2:g.44149849A>T
NC_000007.13:g.44189448A>T
CM000669.1:g.44189448A>T
NC_000007.12:g.44155973A>T
NG_008847.1:g.44575T>A
NG_008847.2:g.53322T>A
ENST00000395796.8:c.*588T>A
ENST00000616242.5:c.590T>A
ENST00000682635.1:n.1076T>A
ENST00000345378.7:c.593T>A
ENST00000403799.8:c.590T>A
ENST00000671824.1:c.590T>A
ENST00000673284.1:c.590T>A
ENST00000345378.6:c.593T>A
ENST00000395796.7:c.587T>A
ENST00000403799.7:c.590T>A
ENST00000437084.1:c.539T>A
ENST00000616242.4:c.587T>A
NM_000162.3:c.590T>A
NM_033507.1:c.593T>A
NM_033508.1:c.587T>A
NM_000162.4:c.590T>A
NM_001354800.1:c.590T>A
NM_033507.2:c.593T>A
NM_033508.2:c.587T>A
NM_000162.5:c.590T>A
NM_033507.3:c.593T>A

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP2 PP3 PS3_Moderate PP4_Moderate

Not Met criteria codes 2

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PM1 PS4

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.590T>A variant in the glucokinase gene, GCK, causes an amino acid change of methionine to lysine at codon 49 (p.(Met197Lys)) 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 v4.1.0 (PM2_Supporting). This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 19790256; internal lab contributors). One of these individuals did have a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative) (PP4_Moderate; PMID: 19790256). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.943, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Additionally, functional studies meeting the MDEP wild type quality control measures showed that the relative activity index (RAI) of this variant was 0.02, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 19336674). In summary, c.590T>A 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): PS3_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (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 0.943, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.02, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 19336674).
PP4_Moderate	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 19790256; internal lab contributors).

Curation History

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