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.497G>C

Version: 1.0

CA367401763

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 3217af19-2337-40f7-b677-acb8e47dd3eb
Approved on: 2026/8/21
Published on: 2026/9/2

HGVS expressions

NM_033508.3:c.497G>C
NC_000007.14:g.44150048C>G
CM000669.2:g.44150048C>G
NC_000007.13:g.44189647C>G
CM000669.1:g.44189647C>G
NC_000007.12:g.44156172C>G
NG_008847.1:g.44376G>C
NG_008847.2:g.53123G>C
ENST00000395796.8:c.*498G>C
ENST00000616242.5:c.500G>C
ENST00000682635.1:n.986G>C
ENST00000345378.7:c.503G>C
ENST00000403799.8:c.500G>C
ENST00000671824.1:c.500G>C
ENST00000673284.1:c.500G>C
ENST00000345378.6:c.503G>C
ENST00000395796.7:c.497G>C
ENST00000403799.7:c.500G>C
ENST00000437084.1:c.449G>C
ENST00000616242.4:c.497G>C
NM_000162.3:c.500G>C
NM_033507.1:c.503G>C
NM_033508.1:c.497G>C
NM_000162.4:c.500G>C
NM_001354800.1:c.500G>C
NM_033507.2:c.503G>C
NM_033508.2:c.497G>C
NM_000162.5:c.500G>C
NM_033507.3:c.503G>C

Likely Pathogenic

Met criteria codes 5

PP4_Moderate | PM5_Supporting | PP2 | PP3 | PM2_Supporting

Not Met criteria codes 3

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PM1 PS4 PP1

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.500G>C variant in the glucokinase gene, GCK, causes an amino acid change of tryptophan to serine at codon 167 (p.(Trp167Ser)) 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 predicted to be deleterious by computational evidence, with a REVEL score of 0.949, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.1 (PM2_Supporting). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). At least 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 antibodies) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (internal lab contributors). Another missense variant at the same residue, c.499T>C (p.Trp167Arg), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.500G>C 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

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 antibodies) (PP4_Moderate; internal lab contributors).
PM5_Supporting	✔	Another missense variant at the same residue, c.499T>C (p.Trp167Arg), has been classified as likely pathogenic by the ClinGen MDEP (PM5_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 0.949, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (PM2_Supporting).

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 two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).

PP1		✖	This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (internal lab contributors).

Curation History

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