

Variant: NM_000162.5(GCK):c.499T>C (p.Trp167Arg)

Version: 1.3

CA367401768 [↗](#)

447408 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

UUID: 8baf769d-4142-48b1-9144-f9044b76b177

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HGVS expressions

NM_000162.5:c.499T>C

NM_000162.5(GCK):c.499T>C (p.Trp167Arg)

NC_000007.14:g.44150049A>G

CM000669.2:g.44150049A>G

NC_000007.13:g.44189648A>G

CM000669.1:g.44189648A>G

NC_000007.12:g.44156173A>G

NG_008847.1:g.44375T>C

NG_008847.2:g.53122T>C

ENST00000395796.8:c.*497T>C

ENST00000616242.5:c.499T>C

ENST00000682635.1:n.985T>C

ENST00000345378.7:c.502T>C

ENST00000403799.8:c.499T>C

ENST00000671824.1:c.499T>C

ENST00000673284.1:c.499T>C

ENST00000345378.6:c.502T>C

ENST00000395796.7:c.496T>C

ENST00000403799.7:c.499T>C

ENST00000437084.1:c.448T>C

ENST00000616242.4:c.496T>C

NM_000162.3:c.499T>C

NM_033507.1:c.502T>C

NM_033508.1:c.496T>C

NM_000162.4:c.499T>C

NM_001354800.1:c.499T>C

NM_033507.2:c.502T>C

NM_033508.2:c.496T>C

NM_033507.3:c.502T>C

NM_033508.3:c.496T>C

Likely Pathogenic

Met criteria codes 5

PS4

PP4_Moderate

PP2

PP3

PM2_Supporting

Not Met criteria codes 1

PM1

Evidence Links 0

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

[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.499T>C variant in the glucokinase gene, GCK, causes an amino acid change of tryptophan to arginine at codon 167 (p.(Trp167Arg)) 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 0.923, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v4.1.1 Grpmax filtering allele frequency due to no more than one copy in any non-founder subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). This variant was identified in eight unrelated individuals with hyperglycemia (PS4; PMID: 21978167, 36257325, ClinVar, internal lab contributors). Additionally, 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). Another missense variant at the same residue, c.501G>C (p.Trp167Cys), has been classified as pathogenic; however, PM5_Supporting was not applied to avoid circularity as p.Trp167Ser contributed to the classification of the other variant at this residue. In summary, c.499T>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): PS4, PP4_Moderate, PM2_Supporting, PP2, PP3.

Met criteria codes

PS4			This variant was identified in eight unrelated individuals with hyperglycemia (PS4; PMID: 36257325, ClinVar, 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 antibodies) (PP4_Moderate; internal lab contributors).
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 0.923, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting			This variant has an incomputable gnomAD v4.1.1 Grpmax filtering allele frequency due to no more than one copy in any non-founder subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (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

Curation History

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