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Variant: NM_000162.5(GCK):c.501G>C (p.Trp167Cys)

Version: 1.0

CA367401759

1685845 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: cb6c6e0b-b90c-4b09-8026-1d3bd0296b97
Approved on: 2026/9/2
Published on: 2026/9/2

HGVS expressions

NM_000162.5(GCK):c.501G>C (p.Trp167Cys)
NM_000162.5:c.501G>C
NC_000007.14:g.44150047C>G
CM000669.2:g.44150047C>G
NC_000007.13:g.44189646C>G
CM000669.1:g.44189646C>G
NC_000007.12:g.44156171C>G
NG_008847.1:g.44377G>C
NG_008847.2:g.53124G>C
ENST00000395796.8:c.*499G>C
ENST00000616242.5:c.501G>C
ENST00000682635.1:n.987G>C
ENST00000345378.7:c.504G>C
ENST00000403799.8:c.501G>C
ENST00000671824.1:c.501G>C
ENST00000673284.1:c.501G>C
ENST00000345378.6:c.504G>C
ENST00000395796.7:c.498G>C
ENST00000403799.7:c.501G>C
ENST00000437084.1:c.450G>C
ENST00000616242.4:c.498G>C
NM_000162.3:c.501G>C
NM_033507.1:c.504G>C
NM_033508.1:c.498G>C
NM_000162.4:c.501G>C
NM_001354800.1:c.501G>C
NM_033507.2:c.504G>C
NM_033508.2:c.498G>C
NM_033507.3:c.504G>C
NM_033508.3:c.498G>C

Pathogenic

Met criteria codes 6

PP4_Moderate PM2_Supporting PM5_Supporting PS2 PP2 PP3

Not Met criteria codes 2

PS4 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.501G>C variant in the glucokinase gene, GCK, causes an amino acid change of tryptophan to cysteine at codon 167 (p.(Trp167Cys)) 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 0.938, 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 three unrelated individuals with hyperglycemia; however, this number is below the ClinGen MDEP threshold for PS4_Moderate (PMID: 34440516, 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; PMID: 34440516, internal lab contributors). This variant was identified as a de novo occurrence with confirmed parental relationships in an individual whose clinical picture is consistent with GCK-hyperglycemia (PS2; 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.501G>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS2, 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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (PM2_Supporting).
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).
PS2	✔	This variant was identified as a de novo occurrence with confirmed parental relationships in an individual whose clinical picture is consistent with GCK-hyperglycemia (PS2; 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 0.938, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

PS4	✖	This variant was identified in three unrelated individuals with hyperglycemia; however, this number is below the ClinGen MDEP threshold for PS4_Moderate (PMID: 34440516, internal lab contributors).
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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