

Variant: *NM_000162.5(GCK):c.89T>C (p.Leu30Pro)*

Version: 1.0

CA10581225 [↗](#)

235097 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 24983182-cc1a-4565-85bd-fb82798f0307

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HGVS expressions

NM_000162.5:c.89T>C

NM_000162.5(GCK):c.89T>C (p.Leu30Pro)

NC_000007.14:g.44153420A>G

CM000669.2:g.44153420A>G

NC_000007.13:g.44193019A>G

CM000669.1:g.44193019A>G

NC_000007.12:g.44159544A>G

NG_008847.1:g.41004T>C

NG_008847.2:g.49751T>C

ENST00000395796.8:c.*87T>C

ENST00000616242.5:c.89T>C

ENST00000682635.1:n.575T>C

ENST00000345378.7:c.92T>C

ENST00000403799.8:c.89T>C

ENST00000671824.1:c.89T>C

ENST00000673284.1:c.89T>C

ENST00000345378.6:c.92T>C

ENST00000395796.7:c.86T>C

ENST00000403799.7:c.89T>C

ENST00000437084.1:c.89T>C

ENST00000476008.1:n.524T>C

ENST00000616242.4:c.86T>C

NM_000162.3:c.89T>C

NM_033507.1:c.92T>C

NM_033508.1:c.86T>C

NM_000162.4:c.89T>C

NM_001354800.1:c.89T>C

NM_033507.2:c.92T>C

NM_033508.2:c.86T>C

NM_033507.3:c.92T>C

NM_033508.3:c.86T>C

Likely Pathogenic

Met criteria codes **6**

PP2

PP3

PS4_Moderate

PM2_Supporting

PS2_Moderate

Expert Panel

Monogenic Diabetes VCEP [↗](#)

PP4_Moderate

Not Met criteria codes 1

PM1

Evidence Links 0

Criteria Specification Information

[Criteria Specification:](#) ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 2.0.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.89T>C variant in the glucokinase gene, GCK, causes an amino acid change of leucine to proline at codon 30 (p.(Leu30Pro)) 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 0.986, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in five individuals with hyperglycemia (PS4_Moderate; PMID: 19564454, 28555465, ClinVar, internal lab contributors). Additionally, 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), and in another individual, the variant was identified as a de novo occurrence with unconfirmed parental relationships (PP4_Moderate, PS2_Moderate; PMID: 28555465, ClinVar). In summary, c.89T>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 2.0.0, approved 2/17/2025): PP2, PP3, PM2_Supporting, PS4_Moderate, PP4_Moderate, PS2_Moderate.

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 0.986, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4_Moderate		✓	This variant was identified in five individuals with hyperglycemia (PS4_Moderate; PMID: 19564454, 28555465, ClinVar, internal lab contributors).
PM2_Supporting		✓	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS2_Moderate		✓	This variant was identified as a de novo occurrence with unconfirmed parental relationships in one individual with a clinical picture consistent with GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PS2_Moderate; PMID: 28555465, ClinVar).
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; PMID: 28555465).

Not Met criteria codes

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

Curation History [↗](#)

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