

Variant: NM_001354803.2:c.269T>C

Version: 1.0

CA367398281 [↗](#)

2734988 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: f9977fe6-8cbb-44b7-a7c2-4566de21ddbc

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HGVS expressions

NM_001354803.2:c.269T>C

NC_000007.14:g.44145515A>G

CM000669.2:g.44145515A>G

NC_000007.13:g.44185114A>G

CM000669.1:g.44185114A>G

NC_000007.12:g.44151639A>G

NG_008847.1:g.48909T>C

NG_008847.2:g.57656T>C

ENST00000395796.8:c.*1233T>C

ENST00000616242.5:c.*355T>C

ENST00000683378.1:n.461T>C

ENST00000336642.9:c.269T>C

ENST00000345378.7:c.1238T>C

ENST00000403799.8:c.1235T>C

ENST00000671824.1:c.1298T>C

ENST00000672743.1:n.247T>C

ENST00000673284.1:c.1235T>C

ENST00000336642.8:c.287T>C

ENST00000345378.6:c.1238T>C

ENST00000395796.7:c.1232T>C

ENST00000403799.7:c.1235T>C

ENST00000437084.1:c.1184T>C

ENST00000459642.1:n.615T>C

ENST00000616242.4:c.1232T>C

NM_000162.3:c.1235T>C

NM_033507.1:c.1238T>C

NM_033508.1:c.1232T>C

NM_000162.4:c.1235T>C

NM_001354800.1:c.1235T>C

NM_001354801.1:c.224T>C

NM_001354802.1:c.95T>C

NM_001354803.1:c.269T>C

NM_033507.2:c.1238T>C

NM_033508.2:c.1232T>C

NM_000162.5:c.1235T>C

NM_033507.3:c.1238T>C

NM_033508.3:c.1232T>C

Pathogenic

Met criteria codes 6

PP2 PP3 PP4 PP1_Strong PM1
PM2_Supporting

Not Met criteria codes 1

PS4

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 1.3.0
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1235T>C variant in the glucokinase gene, GCK, causes an amino acid change of valine to alanine at codon 412 (p.(Val412Ala)) 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 resides in an amino acid that directly binds ATP, which is defined as critical for the protein’s function by the ClinGen MDEP (PM1). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.965, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant segregated with hyperglycemia, with 4 informative meioses in 2 families (PP1_Strong; internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors). 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 (internal lab contributors). In summary, c.1235T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM1, PP2, PP3, PM2_Supporting, PP1_Strong, PP4.

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 0.965, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4		✓	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors).
PP1_Strong		✓	This variant segregated with hyperglycemia, with 4 informative meioses in 2 families (PP1_Strong; internal lab contributors).
PM1		✓	This variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein’s function by the ClinGen MDEP (PM1).
PM2_Supporting		✓	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). absent from gnomAD v4.0.0

Not Met criteria codes

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 (internal lab contributors).

Curation History [↗](#)

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