

Variant: *NM_000162.5(GCK):c.146C>A (p.Thr49Asn)*

Version: 2.0

CA213765 [↗](#)

36204 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 6e333374-f9a3-4a3a-ab78-8cc1941755c5

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HGVS expressions

NM_000162.5:c.146C>A

NM_000162.5(GCK):c.146C>A (p.Thr49Asn)

NC_000007.14:g.44153363G>T

CM000669.2:g.44153363G>T

NC_000007.13:g.44192962G>T

CM000669.1:g.44192962G>T

NC_000007.12:g.44159487G>T

NG_008847.1:g.41061C>A

NG_008847.2:g.49808C>A

ENST00000395796.8:c.*144C>A

ENST00000616242.5:c.146C>A

ENST00000682635.1:n.632C>A

ENST00000345378.7:c.149C>A

ENST00000403799.8:c.146C>A

ENST00000671824.1:c.146C>A

ENST00000673284.1:c.146C>A

ENST00000345378.6:c.149C>A

ENST00000395796.7:c.143C>A

ENST00000403799.7:c.146C>A

ENST00000437084.1:c.146C>A

ENST00000616242.4:c.143C>A

NM_000162.3:c.146C>A

NM_033507.1:c.149C>A

NM_033508.1:c.143C>A

NM_000162.4:c.146C>A

NM_001354800.1:c.146C>A

NM_033507.2:c.149C>A

NM_033508.2:c.143C>A

NM_033507.3:c.149C>A

NM_033508.3:c.143C>A

Pathogenic

Met criteria codes 5

PP4_Moderate

PP2

PP1_Strong

PS4_Moderate

PM2_Supporting

Not Met criteria codes 3

PP3

PS3

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.146C>A variant in the glucokinase gene, GCK causes an amino acid change of threonine to asparagine at codon 49 (p.(Thr49Asn)) 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 has a REVEL score of 0.691, which is between the ClinGen MDEP thresholds for PP3 and BP4, predicting neither a damaging nor benign impact on GCK function. This variant is absent from gnomAD v4.1.2 (PM2_Supporting). This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 30257192, Clinvar, 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% and 3 generation family history of diabetes/hyperglycemia) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia with seven informative meioses in 2 families (PP1_Strong; PMID: 30257192, internal lab contributors). Functional studies demonstrated the p.Thr49Asn protein had a relative activity index (RAI) < 0.5; however, the wild-type kinetic parameters didn't pass the MDEP quality control, and PS3 could not be applied (PMID: 30257192). In summary, this variant meets the criteria to be classified as pathogenic for GCK-MODY. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 3.1.0, approved 10/10/2025): PP1_Strong, PS4_Moderate, PP4_Moderate, PM2_Supporting, PP2.

Met criteria codes

PP4_Moderate

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% and 3 generation family history of diabetes/hyperglycemia) (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).

PP1_Strong

This variant segregated with hyperglycemia with seven informative meioses in 2 families (PP1_Strong; PMID: 30257192, internal lab contributors).

PS4_Moderate

This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 30257192, Clinvar, internal lab contributors).

PM2_Supporting

This variant is absent from gnomAD v4.1.2 (PM2_Supporting).

Not Met criteria codes

