

Variant: *NM_000162.5(GCK):c.764C>T (p.Thr255Ile)*

Version: 1.0

CA367400604 [↗](#)

3720739 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 934f956a-ad7e-482e-b2ec-53721b097062

Approved on: 2025/11/24

Published on: 2025/11/26

HGVS expressions

NM_000162.5(GCK):c.764C>T (p.Thr255Ile)

NM_000162.5:c.764C>T

NC_000007.14:g.44147749G>A

CM000669.2:g.44147749G>A

NC_000007.13:g.44187348G>A

CM000669.1:g.44187348G>A

NC_000007.12:g.44153873G>A

NG_008847.1:g.46675C>T

NG_008847.2:g.55422C>T

ENST00000395796.8:c.*762C>T

ENST00000616242.5:c.764C>T

ENST00000345378.7:c.767C>T

ENST00000403799.8:c.764C>T

ENST00000671824.1:c.764C>T

ENST00000673284.1:c.764C>T

ENST00000345378.6:c.767C>T

ENST00000395796.7:c.761C>T

ENST00000403799.7:c.764C>T

ENST00000437084.1:c.713C>T

ENST00000616242.4:c.761C>T

NM_000162.3:c.764C>T

NM_033507.1:c.767C>T

NM_033508.1:c.761C>T

NM_000162.4:c.764C>T

NM_001354800.1:c.764C>T

NM_033507.2:c.767C>T

NM_033508.2:c.761C>T

NM_033507.3:c.767C>T

NM_033508.3:c.761C>T

Pathogenic

Met criteria codes **8**

PP4_Moderate PM3_Supporting

PM5_Strong PP2 PP3 PM1

PS4_Moderate PM2_Supporting

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Evidence Links 0

[Criteria Specification: ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0](#)

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.764C>T variant in the glucokinase gene, GCK, causes an amino acid change of threonine to isoleucine at codon 255 (p.(Thr255Ile)) of transcript 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 0.795, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein’s function by the ClinGen MDEP (PM1). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate, PMID: 28170077; 19410318; 35472491). Additionally, at least two of these individuals had a linical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L, HbA1c 5.6 - 7.6% and detectable C-peptide in pediatric patients after 3 years) (PP4_Moderate; PMID: 28170077). This variant was also detected in the homozygous state in one individual with neonatal diabetes (PM3_Supporting; PMID: 36510364). Other missense variants at the same residue, c.764C>G (p.Thr255Ser) and c.763A>G (p.Thr255Ala), have been interpreted as pathogenic by the ClinGen MDEP, and p.Thr255Ile has a greater Grantham distance (PM5_Strong). In summary, c.764C>T 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): PM1, PM2_Supporting, PM3_Supporting, PM5_Strong, PP2, PP3, PP4_Moderate, PS4_Moderate.

Met criteria codes

PP4_Moderate			This variant was identified in two individuals with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and positive C-peptide three years post-diagnosis in a pediatric patient) (PP4_Moderate; PMID: 28170077).
PM3_Supporting			This variant has been detected in one individual with neonatal diabetes who was homozygous for this variant (PM3_Supporting; PMID: 3651036).
PM5_Strong			Other missense variants at the same residue, c.764C>G (p.Thr255Ser) and c.763A>G (p.Thr255Ala), have been interpreted as pathogenic by the ClinGen MDEP, and p.Thr255Ile has a greater Grantham distance (PM5_Strong).
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 0.795, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM1			This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein’s function by the ClinGen MDEP (PM1).
PS4_Moderate			This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate, PMID: 28170077; 19410318; 35472491).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting).

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.