

Variant: *NM_000162.5(GCK):c.704T>C (p.Met235Thr)*

Version: 1.0

CA213834 [↗](#)

36248 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: e65ee788-cb00-4d36-b41c-e4e537d41002

Approved on: 2025/9/17

Published on: 2025/9/26

HGVS expressions

NM_000162.5(GCK):c.704T>C (p.Met235Thr)

NM_000162.5:c.704T>C

NC_000007.14:g.44147809A>G

CM000669.2:g.44147809A>G

NC_000007.13:g.44187408A>G

CM000669.1:g.44187408A>G

NC_000007.12:g.44153933A>G

NG_008847.1:g.46615T>C

NG_008847.2:g.55362T>C

ENST00000395796.8:c.*702T>C

ENST00000616242.5:c.704T>C

ENST00000345378.7:c.707T>C

ENST00000403799.8:c.704T>C

ENST00000671824.1:c.704T>C

ENST00000673284.1:c.704T>C

ENST00000345378.6:c.707T>C

ENST00000395796.7:c.701T>C

ENST00000403799.7:c.704T>C

ENST00000437084.1:c.653T>C

ENST00000616242.4:c.701T>C

NM_000162.3:c.704T>C

NM_033507.1:c.707T>C

NM_033508.1:c.701T>C

NM_000162.4:c.704T>C

NM_001354800.1:c.704T>C

NM_033507.2:c.707T>C

NM_033508.2:c.701T>C

NM_033507.3:c.707T>C

NM_033508.3:c.701T>C

Pathogenic

Met criteria codes 8

PM2_Supporting

PP2

PP3

PM5

PS3_Moderate

PP4_Moderate

PS4

PP1_Strong

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Not Met criteria codes 1

PM1

Evidence Links 0

[Criteria Specification: ClinGen Monogenic Diabetes](#)

Expert Panel Specifications to the ACMG/AMP Variant

Interpretation Guidelines for GCK Version 3.0.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.704T>C variant in the glucokinase gene, GCK, causes an amino acid change of methionine to threonine at codon 235 (p.(Met235Thr)) 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 an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.969, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Additionally, MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.21, which is below the MDEP cutoff (<0.5) (PS3_Moderate; Gloyn et al., 2004 (DOI: 10.1159/000079009)). This variant has been indentified in at least 43 individuals with hyperglycemia (PS4; PMID: 19564454, 30592380; internal lab contributors). Furthermore, this variant segregated with hyperglycemia with at least 11 meioses in multiple families (PP1_Strong; internal lab contributors). 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 autoantibodies) (PP4_Moderate; internal lab contributors). Another missense variant at the same residue, c.703A>G (p.Met235Val), has been classified as pathogenic by the ClinGen MDEP and p.Met235Thr has a greater Grantham distance (PM5). In summary, c.704T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.0.0, approved 7/23/2025): PS4, PP1_Strong, PS3_Moderate, PP4_Moderate, PM5, PM2_Supporting, PP2, PP3.

Met criteria codes

PM2_Supporting			This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting.
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 0.969, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5			Another missense variant at the same residue, c.703A>G (p.Met235Val), has been classified as pathogenic by the ClinGen MDEP and p.Met235Thr has a greater Grantham distance (PM5).
PS3_Moderate			MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.21, which is below the MDEP cutoff (<0.5) (PS3_Moderate; Gloyn et al., 2004 (DOI: 10.1159/000079009)).
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 autoantibodies) (PP4_Moderate; internal lab contributors).

PS4			This variant has been indentified in at least 43 individuals with hyperglycemia (PS4; PMID: 19564454, 30592380; internal lab contributors)
PP1_Strong			This variant segregated with hyperglycemia with at least 11 meioses in multiple families (PP1_Strong; internal lab contributors).
Not Met criteria codes			
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 			
			<div><div></div><div>▼</div><div>▼</div></div>
Showing 1 to 1 of 1 rows			
<div></div>			

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.