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Variant: NM_000162.5(GCK):c.671T>C (p.Met224Thr)

Version: 1.0

CA367401149

1464253 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5c26ef0a-a63c-4cd7-a940-c9bfbf7a7c5a
Approved on: 2026/1/22
Published on: 2026/1/28

HGVS expressions

NM_000162.5(GCK):c.671T>C (p.Met224Thr)
NM_000162.5:c.671T>C
NC_000007.14:g.44149768A>G
CM000669.2:g.44149768A>G
NC_000007.13:g.44189367A>G
CM000669.1:g.44189367A>G
NC_000007.12:g.44155892A>G
NG_008847.1:g.44656T>C
NG_008847.2:g.53403T>C
ENST00000395796.8:c.*669T>C
ENST00000616242.5:c.671T>C
ENST00000682635.1:n.1157T>C
ENST00000345378.7:c.674T>C
ENST00000403799.8:c.671T>C
ENST00000671824.1:c.671T>C
ENST00000673284.1:c.671T>C
ENST00000345378.6:c.674T>C
ENST00000395796.7:c.668T>C
ENST00000403799.7:c.671T>C
ENST00000437084.1:c.620T>C
ENST00000616242.4:c.668T>C
NM_000162.3:c.671T>C
NM_033507.1:c.674T>C
NM_033508.1:c.668T>C
NM_000162.4:c.671T>C
NM_001354800.1:c.671T>C
NM_033507.2:c.674T>C
NM_033508.2:c.668T>C
NM_033507.3:c.674T>C
NM_033508.3:c.668T>C

Pathogenic

Met criteria codes 7

PM3_Supporting | PP2 | PP3 | PP1_Strong | PS4 | PP4_Moderate | PM2_Supporting

Not Met criteria codes 1

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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.671T>C variant in the glucokinase gene, GCK, causes an amnio acid change of methionine to threonine at codon 224 (p.(Met224Thr)) of NM_000162.5. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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 0.825, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in at least 12 unrelated individuals with hyperglycemia (PS4; PMID: 11508276, 19790256, 28170077, ClinVar: SCV002318903.1, internal lab contributors). Additionally, at least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (persistent fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% (multiple FBG and HbA1c values in range over time)) (PP4_Moderate; internal lab contributors). This variant was identified in a homozygous state in one individual with neonatal diabetes (PM3_Supporting, internal lab contributors). This variant segregated with hyperglycemia, with at least five informative meioses in two families with MODY (PP1_Strong; internal lab contributors). In summary, c.671T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4, PP1_Strong, PP4_Moderate, PM2_Supporting, PM3_Supporting, PP2, PP3.

Met criteria codes

PM3_Supporting ✔	This variant was identified in a homozygous state in one individual with neonatal diabetes (PM3_Supporting, 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).
PP3 ✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.825, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong ✔	This variant segregated with hyperglycemia, with at least five informative meioses in two families with MODY (PP1_Strong; internal lab contributors).
PS4 ✔	This variant was identified in at least 12 unrelated individuals with hyperglycemia (PS4; PMID: 11508276, 19790256, 28170077, ClinVar: SCV002318903.1, internal lab contributors).
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%; multiple FBG and HbA1c values in range over time) (PP4_Moderate; internal lab contributors).

PM2_Supporting		✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

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

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