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Variant: NM_000162.5(GCK):c.374A>G (p.Tyr125Cys)

Version: 2.0

CA367402194

1705456 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b9327620-8c42-4834-8769-62828aa3bf3c
Approved on: 2026/8/17
Published on: 2026/9/1

HGVS expressions

NM_000162.5:c.374A>G
NM_000162.5(GCK):c.374A>G (p.Tyr125Cys)
NC_000007.14:g.44151065T>C
CM000669.2:g.44151065T>C
NC_000007.13:g.44190664T>C
CM000669.1:g.44190664T>C
NC_000007.12:g.44157189T>C
NG_008847.1:g.43359A>G
NG_008847.2:g.52106A>G
ENST00000395796.8:c.*372A>G
ENST00000616242.5:c.374A>G
ENST00000682635.1:n.860A>G
ENST00000345378.7:c.377A>G
ENST00000403799.8:c.374A>G
ENST00000671824.1:c.374A>G
ENST00000673284.1:c.374A>G
ENST00000345378.6:c.377A>G
ENST00000395796.7:c.371A>G
ENST00000403799.7:c.374A>G
ENST00000437084.1:c.364-41A>G
ENST00000616242.4:c.371A>G
NM_000162.3:c.374A>G
NM_033507.1:c.377A>G
NM_033508.1:c.371A>G
NM_000162.4:c.374A>G
NM_001354800.1:c.374A>G
NM_033507.2:c.377A>G
NM_033508.2:c.371A>G
NM_033507.3:c.377A>G
NM_033508.3:c.371A>G

Likely Pathogenic

Met criteria codes 5

PM2_Supporting | PP2 | PP3 | PP4_Moderate | PP1_Moderate

Not Met criteria codes 2

PM1 | 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 3.1*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.374A>G variant in the glucokinase gene, GCK, causes an amino acid change of tyrosine to cysteine at codon 125 (p.(Tyr125Cys)) 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 is absent from gnomAD v4.1 (PM2_Supporting). Additionally, this variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.977, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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 (PMID: 19790256, ClinVar: 1705456, internal lab contributors). One of these individuals did have a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative autoantibodies as well as a three generation dominant family history of diabetes) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia with four informative meioses in a single family (PP1_Moderate; internal lab contributors). In summary, c.374A>G meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1, approved 10/10/2025): PP4_Moderate, PP1_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (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 0.977, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
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 as well as a three generation dominant family history of diabetes) (PP4_Moderate; internal lab contributors).
PP1_Moderate	✔	This variant segregated with hyperglycemia with four informative meioses in a single family (PP1_Moderate; 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
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 (PMID: 19790256, ClinVar, internal lab contributors).

Curation History

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