

Variant: NM_000162.5(GCK):c.1112G>T (p.Cys371Phe)

Version: 1.0

CA152950 [↗](#)

129140 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 9eb4e0f9-20ec-4efb-bf65-c18791943812

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HGVS expressions

NM_000162.5(GCK):c.1112G>T (p.Cys371Phe)

NM_000162.5:c.1112G>T

NC_000007.14:g.44145638C>A

CM000669.2:g.44145638C>A

NC_000007.13:g.44185237C>A

CM000669.1:g.44185237C>A

NC_000007.12:g.44151762C>A

NG_008847.1:g.48786G>T

NG_008847.2:g.57533G>T

ENST00000395796.8:c.*1110G>T

ENST00000616242.5:c.*232G>T

ENST00000683378.1:n.338G>T

ENST00000336642.9:c.146G>T

ENST00000345378.7:c.1115G>T

ENST00000403799.8:c.1112G>T

ENST00000671824.1:c.1175G>T

ENST00000672743.1:n.124G>T

ENST00000673284.1:c.1112G>T

ENST00000336642.8:c.164G>T

ENST00000345378.6:c.1115G>T

ENST00000395796.7:c.1109G>T

ENST00000403799.7:c.1112G>T

ENST00000437084.1:c.1061G>T

ENST00000459642.1:n.492G>T

ENST00000616242.4:c.1109G>T

NM_000162.3:c.1112G>T

NM_033507.1:c.1115G>T

NM_033508.1:c.1109G>T

NM_000162.4:c.1112G>T

NM_001354800.1:c.1112G>T

NM_001354801.1:c.101G>T

NM_001354802.1:c.-29G>T

NM_001354803.1:c.146G>T

NM_033507.2:c.1115G>T

NM_033508.2:c.1109G>T

NM_033507.3:c.1115G>T

NM_033508.3:c.1109G>T

Pathogenic**Met criteria codes** 6**PS4** **PM2_Supporting** **PP2** **PP3**
PP4_Moderate **PP1_Strong****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 1.0.0*
-  **Criteria Specification Approval History**
-  **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1112G>T variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to phenylalanine at codon 371 (p.(Cys371Phe)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.931, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was hyperglycemia (PS4; PMID 24735133, internal lab contributors). This variant segregated with hyperglycemia with 12 informative meioses in 3 families with MODY (PP1_Strong; internal lab contributors). This variant was identified in at least two individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% as well as either OGTT increment < 3 mmol/L or negative antibodies) (PP4_Moderate; internal lab contributors). In summary, this variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2.0, approved 6/7/2023) : PP2, PP3, PM2_Supporting, PP1_Strong, PS4, PP4_Moderate .

Met criteria codes

PS4			This variant was identified in 9 unrelated individuals with hyperglycemia (PS4; PMID 24735133, internal lab contributors).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (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 0.931, which is [greater than/equal to] the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate			This variant was identified in at least two individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% as well as either OGTT increment < 3 mmol/L or negative antibodies) (PP4_Moderate; internal lab contributors).
PP1_Strong			

This variant segregated with diabetes with 12 informative meioses in 3 families with MODY (PP1_Strong; internal lab contributors).

Curation History [↗](#)

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Showing 1 to 1 of 1 rows

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