The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000162.5(GCK):c.1113C>G (p.Cys371Trp)

Version: 1.0

CA367398928

447379 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: afd68dc6-fb48-483f-9a46-594d8059fb70
Approved on: 2023/8/9
Published on: 2023/8/10

HGVS expressions

NM_000162.5(GCK):c.1113C>G (p.Cys371Trp)
NM_000162.5:c.1113C>G
NC_000007.14:g.44145637G>C
CM000669.2:g.44145637G>C
NC_000007.13:g.44185236G>C
CM000669.1:g.44185236G>C
NC_000007.12:g.44151761G>C
NG_008847.1:g.48787C>G
NG_008847.2:g.57534C>G
ENST00000395796.8:c.*1111C>G
ENST00000616242.5:c.*233C>G
ENST00000683378.1:n.339C>G
ENST00000336642.9:c.147C>G
ENST00000345378.7:c.1116C>G
ENST00000403799.8:c.1113C>G
ENST00000671824.1:c.1176C>G
ENST00000672743.1:n.125C>G
ENST00000673284.1:c.1113C>G
ENST00000336642.8:c.165C>G
ENST00000345378.6:c.1116C>G
ENST00000395796.7:c.1110C>G
ENST00000403799.7:c.1113C>G
ENST00000437084.1:c.1062C>G
ENST00000459642.1:n.493C>G
ENST00000616242.4:c.1110C>G
NM_000162.3:c.1113C>G
NM_033507.1:c.1116C>G
NM_033508.1:c.1110C>G
NM_000162.4:c.1113C>G
NM_001354800.1:c.1113C>G
NM_001354801.1:c.102C>G
NM_001354802.1:c.-28C>G
NM_001354803.1:c.147C>G
NM_033507.2:c.1116C>G
NM_033508.2:c.1110C>G
NM_033507.3:c.1116C>G
NM_033508.3:c.1110C>G

NM_001354803.2:c.147C>G

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PM5 PP4_Moderate PM2_Supporting

Not Met criteria codes 2

PP1 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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1113C>G variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to tryptophan at codon 371 (p.(Cys371Trp)) 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 0.891, 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 identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L and a 3-generation family history of diabetes) (PP4_Moderate; internal lab contributors). This variant was identified in three unrelated individuals with a clinical picture consistent with monogenic diabetes; however, PS4_Moderate cannot be applied because this number is below the MDEP threshold (internal lab contributors). This variant segregated with diabetes with one informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918; internal lab contributors). Another missense variant, c.1112G>T p.(Cys371Phe), has been interpreted as pathogenic by the ClinGen MDEP VCEP and p.Cys371Trp has a greater Grantham distance. (PM5). In summary, this variant meets the criteria to be classified as likely 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, PP4_Moderate, PM5 .

Met criteria codes

PP2	✔	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).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.891, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5	✔	Another missense variant, c.1112G>T p.(Cys371Phe) has been interpreted as pathogenic by the ClinGen MDEP VCEP and p.Cys371Trp has a greater Grantham distance. (PM5).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L and a 3-generation family history of diabetes) (PP4_Moderate; internal lab contributors).

PM2_Supporting		✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PP1		✖	This variant segregated with diabetes with one informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918; internal lab contributors).
PS4		✖	This variant was identified in three unrelated individuals with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold (internal lab contributors).

Curation History

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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.