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.1144T>C (p.Cys382Arg)

Version: 1.0

CA367398754

447384 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e7a5686b-f48c-44b4-b009-039d4f87746f
Approved on: 2023/7/16
Published on: 2023/7/16

HGVS expressions

NM_000162.5(GCK):c.1144T>C (p.Cys382Arg)
NM_000162.5:c.1144T>C
NC_000007.14:g.44145606A>G
CM000669.2:g.44145606A>G
NC_000007.13:g.44185205A>G
CM000669.1:g.44185205A>G
NC_000007.12:g.44151730A>G
NG_008847.1:g.48818T>C
NG_008847.2:g.57565T>C
ENST00000395796.8:c.*1142T>C
ENST00000616242.5:c.*264T>C
ENST00000683378.1:n.370T>C
ENST00000336642.9:c.178T>C
ENST00000345378.7:c.1147T>C
ENST00000403799.8:c.1144T>C
ENST00000671824.1:c.1207T>C
ENST00000672743.1:n.156T>C
ENST00000673284.1:c.1144T>C
ENST00000336642.8:c.196T>C
ENST00000345378.6:c.1147T>C
ENST00000395796.7:c.1141T>C
ENST00000403799.7:c.1144T>C
ENST00000437084.1:c.1093T>C
ENST00000459642.1:n.524T>C
ENST00000616242.4:c.1141T>C
NM_000162.3:c.1144T>C
NM_033507.1:c.1147T>C
NM_033508.1:c.1141T>C
NM_000162.4:c.1144T>C
NM_001354800.1:c.1144T>C
NM_001354801.1:c.133T>C
NM_001354802.1:c.4T>C
NM_001354803.1:c.178T>C
NM_033507.2:c.1147T>C
NM_033508.2:c.1141T>C
NM_033507.3:c.1147T>C
NM_033508.3:c.1141T>C

NM_001354803.2:c.178T>C

Pathogenic

Met criteria codes 6

PP4_Moderate | PM5_Supporting | PS4 | PP2 | PP3 | PM2_Supporting

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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1144T>C variant in the glucokinase gene, GCK, causes an amino acid change of Cys to Arg at codon 382 (p.(Cys382Arg)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (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 0.967 which is greater than the MDEP VCEP threshold of 0.70 (PP3). Another missense variant, c.1144T>G p.Cys382Gly, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 3 generation family history of diabetes) (PP4_Moderate; internal lab contributors). This variant was identified in 7 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID:24804978, Zubkova N.A et al, World J PM. 2017;1(1):40-48. https://doi.org/10.14341/WJPM9298, internal lab contributors). In summary, c.1144T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PP2, PP3, PM2_Supporting, PM5_Supporting, PP4_Moderate, PS4.

Met criteria codes

PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and a 3 generation family history of diabetes) (PP4_Moderate; internal lab contributors).
PM5_Supporting	✔	Another missense variant, c.1144T>G p.Cys382Gly, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
PS4	✔	This variant was identified in 7 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID:24804978, Zubkova N.A et al, World J PM. 2017;1(1):40-48. https://doi.org/10.14341/WJPM9298, 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 0.967 which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).

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

Curation History

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