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.1145G>A (p.Cys382Tyr)

Version: 1.0

CA367398751

1256304 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b17e0692-a2da-4e76-9e2b-b28ed6772784
Approved on: 2023/7/16
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HGVS expressions

NM_000162.5(GCK):c.1145G>A (p.Cys382Tyr)
NM_000162.5:c.1145G>A
NC_000007.14:g.44145605C>T
CM000669.2:g.44145605C>T
NC_000007.13:g.44185204C>T
CM000669.1:g.44185204C>T
NC_000007.12:g.44151729C>T
NG_008847.1:g.48819G>A
NG_008847.2:g.57566G>A
ENST00000395796.8:c.*1143G>A
ENST00000616242.5:c.*265G>A
ENST00000683378.1:n.371G>A
ENST00000336642.9:c.179G>A
ENST00000345378.7:c.1148G>A
ENST00000403799.8:c.1145G>A
ENST00000671824.1:c.1208G>A
ENST00000672743.1:n.157G>A
ENST00000673284.1:c.1145G>A
ENST00000336642.8:c.197G>A
ENST00000345378.6:c.1148G>A
ENST00000395796.7:c.1142G>A
ENST00000403799.7:c.1145G>A
ENST00000437084.1:c.1094G>A
ENST00000459642.1:n.525G>A
ENST00000616242.4:c.1142G>A
NM_000162.3:c.1145G>A
NM_033507.1:c.1148G>A
NM_033508.1:c.1142G>A
NM_000162.4:c.1145G>A
NM_001354800.1:c.1145G>A
NM_001354801.1:c.134G>A
NM_001354802.1:c.5G>A
NM_001354803.1:c.179G>A
NM_033507.2:c.1148G>A
NM_033508.2:c.1142G>A
NM_033507.3:c.1148G>A
NM_033508.3:c.1142G>A

NM_001354803.2:c.179G>A

Pathogenic

Met criteria codes 7

PM2_Supporting PS4 PM5 PP1 PP2 PP3 PP4

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.1145G>A variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to tyrosine at codon 382 (p.(Cys382Tyr)) 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 0.922 which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in the homozygous state in three individuals with neonatal diabetes and negative testing for ABCC8, KCNJ11, and INS (internal lab contributors). This variant segregated with diabetes, with 3 informative meioses in 1 family with MODY (PP1; internal lab contributors). Another missense variant, c.1144T>C p.Cys382Arg, has been interpreted as pathogenic by the ClinGen MDEP, and p.Cys382Tyr has a greater Grantham distance (PM5). This variant was identified in 7 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; 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.1145G>A 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): PP1, PP2, PP3, PM2_Supporting, PM5, PP4, PS4.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4	✔	This variant was identified in 7 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; Zubkova N.A et al, World J PM. 2017;1(1):40-48. https://doi.org/10.14341/WJPM9298, internal lab contributors).
PM5	✔	Another missense variant, c.1144T>C p.Cys382Arg, has been interpreted as pathogenic by the ClinGen MDEP, and p.Cys382Tyr has a greater Grantham distance (PM5).
PP1	✔	This variant segregated with diabetes, with 3 informative meioses in 1 family with MODY (PP1; 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 0.922 which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PP4		✔	This variant was identified in the homozygous state in three individuals with neonatal diabetes and negative testing for ABCC8, KCNJ11, and INS (internal lab contributors).

Curation History

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