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.1174C>T (p.Arg392Cys)

Version: 1.0

CA367398622

585909 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0e01d1e0-cdee-4782-ab8d-766899ffa48f
Approved on: 2023/7/16
Published on: 2023/7/16

HGVS expressions

NM_000162.5(GCK):c.1174C>T (p.Arg392Cys)
NM_000162.5:c.1174C>T
NC_000007.14:g.44145576G>A
CM000669.2:g.44145576G>A
NC_000007.13:g.44185175G>A
CM000669.1:g.44185175G>A
NC_000007.12:g.44151700G>A
NG_008847.1:g.48848C>T
NG_008847.2:g.57595C>T
ENST00000395796.8:c.*1172C>T
ENST00000616242.5:c.*294C>T
ENST00000683378.1:n.400C>T
ENST00000336642.9:c.208C>T
ENST00000345378.7:c.1177C>T
ENST00000403799.8:c.1174C>T
ENST00000671824.1:c.1237C>T
ENST00000672743.1:n.186C>T
ENST00000673284.1:c.1174C>T
ENST00000336642.8:c.226C>T
ENST00000345378.6:c.1177C>T
ENST00000395796.7:c.1171C>T
ENST00000403799.7:c.1174C>T
ENST00000437084.1:c.1123C>T
ENST00000459642.1:n.554C>T
ENST00000616242.4:c.1171C>T
NM_000162.3:c.1174C>T
NM_033507.1:c.1177C>T
NM_033508.1:c.1171C>T
NM_000162.4:c.1174C>T
NM_001354800.1:c.1174C>T
NM_001354801.1:c.163C>T
NM_001354802.1:c.34C>T
NM_001354803.1:c.208C>T
NM_033507.2:c.1177C>T
NM_033508.2:c.1171C>T
NM_033507.3:c.1177C>T
NM_033508.3:c.1171C>T

NM_001354803.2:c.208C>T

Pathogenic

Met criteria codes 6

PP1_Strong PM2_Supporting PS4 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.1174C>T variant in the glucokinase gene, GCK, causes an amino acid change of Arg to Cys at codon 392 (p.(Arg392Cys)) 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 0.911 which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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%) (PP4; internal lab contributors). This variant was identified in 15 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID:29758564 , internal lab contributors). This variant segregated with diabetes/hyperglycemia, with at least 19 informative meioses in 10 families with MODY (PP1_Strong; internal lab contributors). In summary, c.1174C>T 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): PM2_Supporting, PP2, PP3, PP4, PS4, PP1_Strong.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes, with at least 19 informative meioses in 10 families with MODY (PP1_Strong; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4	✔	This variant was identified in 15 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID:29758564 , 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 0.911 which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PP4	✔	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%) (PP4; internal lab contributors).

Curation History

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