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.1190G>A (p.Arg397His)

Version: 1.0

CA367398533

995102 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: maturity-onset diabetes of the young type 2 (MONDO:0007453)
Inheritance Mode: Autosomal dominant inheritance
UUID: 061baf7c-d594-4729-a388-afa5ae6964c4
Approved on: 2023/9/8
Published on: 2023/9/8

HGVS expressions

NM_000162.5(GCK):c.1190G>A (p.Arg397His)
NM_000162.5:c.1190G>A
NC_000007.14:g.44145560C>T
CM000669.2:g.44145560C>T
NC_000007.13:g.44185159C>T
CM000669.1:g.44185159C>T
NC_000007.12:g.44151684C>T
NG_008847.1:g.48864G>A
NG_008847.2:g.57611G>A
ENST00000395796.8:c.*1188G>A
ENST00000616242.5:c.*310G>A
ENST00000683378.1:n.416G>A
ENST00000336642.9:c.224G>A
ENST00000345378.7:c.1193G>A
ENST00000403799.8:c.1190G>A
ENST00000671824.1:c.1253G>A
ENST00000672743.1:n.202G>A
ENST00000673284.1:c.1190G>A
ENST00000336642.8:c.242G>A
ENST00000345378.6:c.1193G>A
ENST00000395796.7:c.1187G>A
ENST00000403799.7:c.1190G>A
ENST00000437084.1:c.1139G>A
ENST00000459642.1:n.570G>A
ENST00000616242.4:c.1187G>A
NM_000162.3:c.1190G>A
NM_033507.1:c.1193G>A
NM_033508.1:c.1187G>A
NM_000162.4:c.1190G>A
NM_001354800.1:c.1190G>A
NM_001354801.1:c.179G>A
NM_001354802.1:c.50G>A
NM_001354803.1:c.224G>A
NM_033507.2:c.1193G>A
NM_033508.2:c.1187G>A
NM_033507.3:c.1193G>A
NM_033508.3:c.1187G>A

NM_001354803.2:c.224G>A

Likely Pathogenic

Met criteria codes 7

PS4_Moderate PM5_Supporting PM2_Supporting 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.1190G>A variant in the glucokinase gene, GCK, causes an amino acid change of Arg to His at codon 397 (p.(Arg397His)) of NM_000162.5. Another missense variant, c.1190G>T p.Arg397Leu, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Arg397His (PM5_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 absent from gnomAD v2.1.1 (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.779 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 5 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors). This variant segregated with diabetes/hyperglycemia, with 2 informative meioses in 2 families with MODY (PP1; internal lab contributors). In summary, c.1190G>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM5_Supporting, PP2, PM2_Supporting, PP3, PP4, PS4_Moderate, PP1.

Met criteria codes

PS4_Moderate	✔	This variant was identified in 5 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors).
PM5_Supporting	✔	Another missense variant, c.1190G>T p.Arg397Leu, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Arg397His (PM5_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP1	✔	This variant segregated with diabetes/hyperglycemia, with 2 informative meioses in 2 families 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 0.779 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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