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.1181G>T (p.Arg394Leu)

Version: 2.1

CA367398578

1522625 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7b717baa-5df4-4bbc-8132-edfcceb7b495
Approved on: 2025/4/25
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HGVS expressions

NM_000162.5:c.1181G>T
NM_000162.5(GCK):c.1181G>T (p.Arg394Leu)
NC_000007.14:g.44145569C>A
CM000669.2:g.44145569C>A
NC_000007.13:g.44185168C>A
CM000669.1:g.44185168C>A
NC_000007.12:g.44151693C>A
NG_008847.1:g.48855G>T
NG_008847.2:g.57602G>T
ENST00000395796.8:c.*1179G>T
ENST00000616242.5:c.*301G>T
ENST00000683378.1:n.407G>T
ENST00000336642.9:c.215G>T
ENST00000345378.7:c.1184G>T
ENST00000403799.8:c.1181G>T
ENST00000671824.1:c.1244G>T
ENST00000672743.1:n.193G>T
ENST00000673284.1:c.1181G>T
ENST00000336642.8:c.233G>T
ENST00000345378.6:c.1184G>T
ENST00000395796.7:c.1178G>T
ENST00000403799.7:c.1181G>T
ENST00000437084.1:c.1130G>T
ENST00000459642.1:n.561G>T
ENST00000616242.4:c.1178G>T
NM_000162.3:c.1181G>T
NM_033507.1:c.1184G>T
NM_033508.1:c.1178G>T
NM_000162.4:c.1181G>T
NM_001354800.1:c.1181G>T
NM_001354801.1:c.170G>T
NM_001354802.1:c.41G>T
NM_001354803.1:c.215G>T
NM_033507.2:c.1184G>T
NM_033508.2:c.1178G>T
NM_033507.3:c.1184G>T
NM_033508.3:c.1178G>T

NM_001354803.2:c.215G>T

Likely Pathogenic

Met criteria codes 6

PP4_Moderate PM5_Supporting PP2 PP3 PM2_Supporting PS3_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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1181G>T variant in the glucokinase gene, GCK, causes an amino acid change of arginine to leucine at codon 394 (p.(Arg394Leu)) of transcript NM_000162.5. This variant is absent from gnomAD v4.1 (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 0.925 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% and three generation family history of diabetes/hyperglycemia) (PP4_Moderate; internal lab contributors). While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the relative stability index was below the MDEP cutoff of 0.5 (PS3_Supporting; internal lab contributors). Another missense variant at the same amino acid position, c.1181G>C p.Arg394Pro has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.1181G>T meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 2/17/2025): PM2_Supporting, PP2, PP3, PP4_Moderate, PS3_Supporting, PM5_Supporting.

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, HbA1c 5.6 - 7.6%, and three generation family history of diabetes/hyperglycemia) (PP4_Moderate; internal lab contributors).
PM5_Supporting	✔	Another missense variant at the same amino acid position, c.1181G>C p.Arg394Pro has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
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 0.801, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

PS3_Supporting		✔	While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the relative stability index was below the MDEP cutoff of 0.5 (PS3_Supporting; internal lab contributors).

Curation History

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