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Variant: NM_000162.5(GCK):c.1181G>C (p.Arg394Pro)

Version: 2.0

CA367398581

2169517 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: bb53053f-9f55-45c8-90ae-bd1ac0c7d3af
Approved on: 2025/4/22
Published on: 2025/4/23

HGVS expressions

NM_000162.5:c.1181G>C
NM_000162.5(GCK):c.1181G>C (p.Arg394Pro)
NC_000007.14:g.44145569C>G
CM000669.2:g.44145569C>G
NC_000007.13:g.44185168C>G
CM000669.1:g.44185168C>G
NC_000007.12:g.44151693C>G
NG_008847.1:g.48855G>C
NG_008847.2:g.57602G>C
ENST00000395796.8:c.*1179G>C
ENST00000616242.5:c.*301G>C
ENST00000683378.1:n.407G>C
ENST00000336642.9:c.215G>C
ENST00000345378.7:c.1184G>C
ENST00000403799.8:c.1181G>C
ENST00000671824.1:c.1244G>C
ENST00000672743.1:n.193G>C
ENST00000673284.1:c.1181G>C
ENST00000336642.8:c.233G>C
ENST00000345378.6:c.1184G>C
ENST00000395796.7:c.1178G>C
ENST00000403799.7:c.1181G>C
ENST00000437084.1:c.1130G>C
ENST00000459642.1:n.561G>C
ENST00000616242.4:c.1178G>C
NM_000162.3:c.1181G>C
NM_033507.1:c.1184G>C
NM_033508.1:c.1178G>C
NM_000162.4:c.1181G>C
NM_001354800.1:c.1181G>C
NM_001354801.1:c.170G>C
NM_001354802.1:c.41G>C
NM_001354803.1:c.215G>C
NM_033507.2:c.1184G>C
NM_033508.2:c.1178G>C
NM_033507.3:c.1184G>C
NM_033508.3:c.1178G>C

NM_001354803.2:c.215G>C

Likely Pathogenic

Met criteria codes 6

PS4_Moderate PP1 PP2 PP3 PP4_Moderate 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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1181G>C variant in the glucokinase gene, GCK, causes an amino acid change of alanine to proline at codon 394 (p.(Arg394Pro)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.851, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1 (PM2_Supporting). 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 OGTT increment < 3 mmol/L)(PP4_Moderate; internal lab contributors). This variant was identified in four unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors). Additionally, it segregated with diabetes with 2 informative meioses in 2 families (PP1; internal lab contributors). In summary, c.1181G>C 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): PP1, PP2, PP3, PP4_Moderate, PM2_Supporting, PS4_Moderate.

Met criteria codes

PS4_Moderate	✔	This variant was identified in four unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors)
PP1	✔	This variant segregated with diabetes with 2 informative meioses in 2 families (PP1; internal lab contributors).
PP2	✔	GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.851, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
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 OGTT increment < 3 mmol/L)(PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Curation History

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