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_001354803.2:c.214C>A

Version: 2.0

CA367398584

3602130 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 8cccfeae-f8ba-4593-8678-40ca8a2b7957
Approved on: 2025/4/21
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HGVS expressions

NM_001354803.2:c.214C>A
NC_000007.14:g.44145570G>T
CM000669.2:g.44145570G>T
NC_000007.13:g.44185169G>T
CM000669.1:g.44185169G>T
NC_000007.12:g.44151694G>T
NG_008847.1:g.48854C>A
NG_008847.2:g.57601C>A
ENST00000395796.8:c.*1178C>A
ENST00000616242.5:c.*300C>A
ENST00000683378.1:n.406C>A
ENST00000336642.9:c.214C>A
ENST00000345378.7:c.1183C>A
ENST00000403799.8:c.1180C>A
ENST00000671824.1:c.1243C>A
ENST00000672743.1:n.192C>A
ENST00000673284.1:c.1180C>A
ENST00000336642.8:c.232C>A
ENST00000345378.6:c.1183C>A
ENST00000395796.7:c.1177C>A
ENST00000403799.7:c.1180C>A
ENST00000437084.1:c.1129C>A
ENST00000459642.1:n.560C>A
ENST00000616242.4:c.1177C>A
NM_000162.3:c.1180C>A
NM_033507.1:c.1183C>A
NM_033508.1:c.1177C>A
NM_000162.4:c.1180C>A
NM_001354800.1:c.1180C>A
NM_001354801.1:c.169C>A
NM_001354802.1:c.40C>A
NM_001354803.1:c.214C>A
NM_033507.2:c.1183C>A
NM_033508.2:c.1177C>A
NM_000162.5:c.1180C>A
NM_033507.3:c.1183C>A
NM_033508.3:c.1177C>A

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP2 PP3 PP4_Moderate PM5_Supporting

Not Met criteria codes 2

PM1 PS4

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.1180C>A variant in the glucokinase gene, GCK, causes an amino acid change of arginine to serine at codon 394 (p.(Arg394Ser)) of NM_000162.5. 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 0.773, 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 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 28323911, internal lab contributors). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 2 hour OGTT increment < 3 mmol/L and negative antibodies) (PP4_Moderate; internal lab contributors). Another missense variant, c.1181G>C p.Arg394Pro has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.1180C>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 2.0.0, approved 2/17/2025): PP4_Moderate, PP2, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_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 0.773, which is greater than 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-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 2 hour OGTT increment < 3 mmol/L and negative antibodies) (PP4_Moderate; internal lab contributors).
PM5_Supporting	✔	Another missense variant, c.1181G>C p.Arg394Pro has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant was identified in 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 28323911, internal lab contributors).

Curation History

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