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.185C>G

Version: 2.0

CA367398723

3901863 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: c837d53f-7b31-440a-81cc-7aa668fb8481
Approved on: 2026/9/1
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HGVS expressions

NM_001354803.2:c.185C>G
NC_000007.14:g.44145599G>C
CM000669.2:g.44145599G>C
NC_000007.13:g.44185198G>C
CM000669.1:g.44185198G>C
NC_000007.12:g.44151723G>C
NG_008847.1:g.48825C>G
NG_008847.2:g.57572C>G
ENST00000395796.8:c.*1149C>G
ENST00000616242.5:c.*271C>G
ENST00000683378.1:n.377C>G
ENST00000336642.9:c.185C>G
ENST00000345378.7:c.1154C>G
ENST00000403799.8:c.1151C>G
ENST00000671824.1:c.1214C>G
ENST00000672743.1:n.163C>G
ENST00000673284.1:c.1151C>G
ENST00000336642.8:c.203C>G
ENST00000345378.6:c.1154C>G
ENST00000395796.7:c.1148C>G
ENST00000403799.7:c.1151C>G
ENST00000437084.1:c.1100C>G
ENST00000459642.1:n.531C>G
ENST00000616242.4:c.1148C>G
NM_000162.3:c.1151C>G
NM_033507.1:c.1154C>G
NM_033508.1:c.1148C>G
NM_000162.4:c.1151C>G
NM_001354800.1:c.1151C>G
NM_001354801.1:c.140C>G
NM_001354802.1:c.11C>G
NM_001354803.1:c.185C>G
NM_033507.2:c.1154C>G
NM_033508.2:c.1148C>G
NM_000162.5:c.1151C>G
NM_033507.3:c.1154C>G
NM_033508.3:c.1148C>G

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

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 3.1*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1151C>G variant in the glucokinase gene, GCK, causes an amino acid change of alanine to glycine at codon 384 (p.(Ala384Gly)) 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 absent from gnomAD v4.1.1 (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.86, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). One of these individuals did have a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). Another missense variant at the same codon, c.1151C>A (p.Ala384Glu), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ala384Gly (PM5_Supporting). In summary, c.1151C>G meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PP4_Moderate, PM2_Supporting, PP2, PP3, PM5_Supporting.

Met criteria codes

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 0.86, 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 (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant at the same codon, c.1151C>A (p.Ala384Glu), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ala384Gly (PM5_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).

Curation History

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