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.89T>G

Version: 1.0

CA367399229

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7dac75cf-b5da-4a5b-a24e-3dd909cf7a93
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HGVS expressions

NM_001354803.2:c.89T>G
NC_000007.14:g.44145695A>C
CM000669.2:g.44145695A>C
NC_000007.13:g.44185294A>C
CM000669.1:g.44185294A>C
NC_000007.12:g.44151819A>C
NG_008847.1:g.48729T>G
NG_008847.2:g.57476T>G
ENST00000395796.8:c.*1053T>G
ENST00000616242.5:c.*175T>G
ENST00000683378.1:n.281T>G
ENST00000336642.9:c.89T>G
ENST00000345378.7:c.1058T>G
ENST00000403799.8:c.1055T>G
ENST00000671824.1:c.1118T>G
ENST00000672743.1:n.67T>G
ENST00000673284.1:c.1055T>G
ENST00000336642.8:c.107T>G
ENST00000345378.6:c.1058T>G
ENST00000395796.7:c.1052T>G
ENST00000403799.7:c.1055T>G
ENST00000437084.1:c.1004T>G
ENST00000459642.1:n.435T>G
ENST00000473353.1:n.353T>G
ENST00000616242.4:c.1052T>G
NM_000162.3:c.1055T>G
NM_033507.1:c.1058T>G
NM_033508.1:c.1052T>G
NM_000162.4:c.1055T>G
NM_001354800.1:c.1055T>G
NM_001354801.1:c.44T>G
NM_001354802.1:c.-86T>G
NM_001354803.1:c.89T>G
NM_033507.2:c.1058T>G
NM_033508.2:c.1052T>G
NM_000162.5:c.1055T>G
NM_033507.3:c.1058T>G

NM_033508.3:c.1052T>G

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

PP1

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.1055T>G variant in the glucokinase gene, GCK, causes an amino acid change of leucine to arginine at codon 352 (p.(Leu352Arg)) 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 v4.1.0 genomes (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.994, 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-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and a 3 generation dominant family history of hyperglycemia) (PP4_Moderate; PMID: 24804978). This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, 24804978). Another missense variant at the same residue, c.1055T>C (p.Leu352Pro), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.1055T>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 2.0.0, approved 2/17/2025): PP2, PP3, PM2_Supporting, PP4_Moderate, 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 0.994, 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 a 3 generation dominant family history of hyperglycemia) (PP4_Moderate; PMID: 24804978).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant at the same residue, c.1055T>C (p.Leu352Pro), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).

Not Met criteria codes

PP1	✖	This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, 24804978).

Curation History

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