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Variant: NM_001354803.2:c.200T>C

Version: 2.0

CA367398657

3233998 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: bad035fa-80a7-4d1b-9b50-d319d9b30970
Approved on: 2026/4/28
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HGVS expressions

NM_001354803.2:c.200T>C
NC_000007.14:g.44145584A>G
CM000669.2:g.44145584A>G
NC_000007.13:g.44185183A>G
CM000669.1:g.44185183A>G
NC_000007.12:g.44151708A>G
NG_008847.1:g.48840T>C
NG_008847.2:g.57587T>C
ENST00000395796.8:c.*1164T>C
ENST00000616242.5:c.*286T>C
ENST00000683378.1:n.392T>C
ENST00000336642.9:c.200T>C
ENST00000345378.7:c.1169T>C
ENST00000403799.8:c.1166T>C
ENST00000671824.1:c.1229T>C
ENST00000672743.1:n.178T>C
ENST00000673284.1:c.1166T>C
ENST00000336642.8:c.218T>C
ENST00000345378.6:c.1169T>C
ENST00000395796.7:c.1163T>C
ENST00000403799.7:c.1166T>C
ENST00000437084.1:c.1115T>C
ENST00000459642.1:n.546T>C
ENST00000616242.4:c.1163T>C
NM_000162.3:c.1166T>C
NM_033507.1:c.1169T>C
NM_033508.1:c.1163T>C
NM_000162.4:c.1166T>C
NM_001354800.1:c.1166T>C
NM_001354801.1:c.155T>C
NM_001354802.1:c.26T>C
NM_001354803.1:c.200T>C
NM_033507.2:c.1169T>C
NM_033508.2:c.1163T>C
NM_000162.5:c.1166T>C
NM_033507.3:c.1169T>C
NM_033508.3:c.1163T>C

Likely Pathogenic

Met criteria codes 5

PP4_Moderate | PM2_Supporting | PM5_Supporting | PP2 | PP3

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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1166T>C variant in the glucokinase gene, GCK, causes an amino acid change of valine to alanine at codon 389 (p.(Val389Ala)) 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 0.956, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.0 (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: 19790256). 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 a four generation dominant family history of diabetes) (PP4_Moderate; internal lab contributors). Another missense variant, c.1166T>A p.Val389Asp, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.1166T>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 3.1.0approved 10/10/2025): PP4_Moderate, PP2, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

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 four generation dominant family history of diabetes) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.1166T>A p.Val389Asp, 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 0.956, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

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: 19790256).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001354803.2:c.200T>C	Likely Pathogenic	Monogenic Diabetes	2026-04-28	2.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0	GCK
View	NM_001354803.2:c.200T>C	Uncertain Significance	Monogenic Diabetes	2024-04-28	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0	GCK

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