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.200T>A*

Version: 1.1

*CA367398660*

**Gene**: GCK (HGNC:2645)
**Condition**: monogenic diabetes (MONDO:0015967)
**Inheritance Mode**: Semidominant inheritance
**UUID:** c490d374-e64e-4306-b284-be7e91e050d8
**Approved on**: 2024/6/22
**Published on**: 2024/6/22

## *HGVS expressions*

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

**Likely Pathogenic**

**Met criteria codes** 5

PM2_Supporting PP2 PP3 PP4 PS3_Moderate

**Not Met criteria codes** 2

PP1 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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Monogenic Diabetes VCEP***

**The c.1166T>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to aspartic acid at codon 389 (p.(Val389Asp)) 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 0.961, which is greater than the MDEP VCEP threshold of 0.70 (PP3). MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be <0.1, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 2145522). This variant is absent from gnomAD v2.1.1 (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 (PMIDs: 23771925, 32741144, internal lab contributors). This variant segregated with hyperglycemia with 1 informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (internal lab contributors). In summary, c.1166T>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 1.3.0 approved 8/11/2023): PS3_Moderate, PP2, PP3, PP4, PM2_Supporting.**

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**Met criteria codes**

| | | |
|---|---|---|
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v2.1.1 (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 0.961, which is greater than the MDEP VCEP threshold of 0.70 (PP3). |
| **PP4** | ✔ | 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%) (PP4; internal lab contributors). |
| **PS3_Moderate** | ✔ | MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be <0.1, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 2145522). |

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**Not Met criteria codes**

| | | |
|---|---|---|
| **PP1** | ✖ | This variant segregated with hyperglycemia with 1 informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (internal lab contributors). |
| **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 (PMIDs: 23771925, 32741144, internal lab contributors). |

Curation History

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