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.182C>G*

Version: 1.0

*CA367398735*

*3024418 (ClinVar)*

**Gene**: GCK (HGNC:2645)
**Condition**: monogenic diabetes (MONDO:0015967)
**Inheritance Mode**: Semidominant inheritance
**UUID:** d4bc58a6-cf17-49c5-97ce-635f8988c4b9
**Approved on**: 2024/2/28
**Published on**: 2024/2/28

## *HGVS expressions*

**NM_001354803.2:c.182C>G**
NC_000007.14:g.44145602G>C
CM000669.2:g.44145602G>C
NC_000007.13:g.44185201G>C
CM000669.1:g.44185201G>C
NC_000007.12:g.44151726G>C
NG_008847.1:g.48822C>G
NG_008847.2:g.57569C>G
ENST00000395796.8:c.*1146C>G
ENST00000616242.5:c.*268C>G
ENST00000683378.1:n.374C>G
ENST00000336642.9:c.182C>G
ENST00000345378.7:c.1151C>G
ENST00000403799.8:c.1148C>G
ENST00000671824.1:c.1211C>G
ENST00000672743.1:n.160C>G
ENST00000673284.1:c.1148C>G
ENST00000336642.8:c.200C>G
ENST00000345378.6:c.1151C>G
ENST00000395796.7:c.1145C>G
ENST00000403799.7:c.1148C>G
ENST00000437084.1:c.1097C>G
ENST00000459642.1:n.528C>G
ENST00000616242.4:c.1145C>G
NM_000162.3:c.1148C>G
NM_033507.1:c.1151C>G
NM_033508.1:c.1145C>G
NM_000162.4:c.1148C>G
NM_001354800.1:c.1148C>G
NM_001354801.1:c.137C>G
NM_001354802.1:c.8C>G
NM_001354803.1:c.182C>G
NM_033507.2:c.1151C>G
NM_033508.2:c.1145C>G
NM_000162.5:c.1148C>G
NM_033507.3:c.1151C>G
NM_033508.3:c.1145C>G

**Likely Pathogenic**

**Met criteria codes** 5

PP1_Moderate | PM2_Supporting | PM5 | PP2 | PP3

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.1148C>G variant in the glucokinase gene, GCK, causes an amino acid change of serine to tryptophan at codon 383 (p. (Ser383Trp)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 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 located in the larger hexokinase domain of the GCK gene (PMID: 31638168) but this variant does not reside in an amino acid that directly binds glucose or ATP, which is defined as critical for the protein's function by the ClinGen MDEP, so it does not meet PM1. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.85 which is greater than the MDEP VCEP threshold of 0.70 (PP3). Another missense variant, c.1148C>T (p.Ser383Leu), has been interpreted as pathogenic by the ClinGen MDEP, and p.Ser383Trp has an equal or greater Grantham distance (PM5). This variant was found in one family, and segregated with hyperglycemia, with four informative meioses (PP1_Moderate; PMID: 3385223). In summary, c.1148C>G meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (VCEP specifications version v1.3.0; approved 8/11/2023): PP3, PP2, PP1_Moderate, PM5, PM2_Supporting**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1_Moderate** | ✔ | This variant segregated with hyperglycemia, with four informative meioses in one family (PP1_Moderate; PMID: 3385223). |
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v2.1.1 (PM2_Supporting). |
| **PM5** | ✔ | Another missense variant, c.1148C>T (p.Ser383Leu), has been interpreted as pathogenic by the ClinGen MDEP, and p.Ser383Trp has an equal or greater Grantham distance (PM5). |
| **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** | ✔ | REVEL 0.85 |

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
⌑ Powered by BCM's Genboree.