

Variant: *NM\_000162.5(GCK):c.1133C>G (p.Ala378Gly)*

Version: 1.0

CA367398802 [↗](#)

972776 (ClinVar) [↗](#)

**Gene:** GCK ([HGNC:2645](#))

**Condition:** monogenic diabetes ([MONDO:0015967](#))

**Inheritance Mode:** Semidominant inheritance

**UUID:** e241b715-2524-4df2-8eca-9f8e1b9d8ff6

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### *HGVS expressions*

**NM\_000162.5(GCK):c.1133C>G (p.Ala378Gly)**

**NM\_000162.5:c.1133C>G**

NC\_000007.14:g.44145617G>C

CM000669.2:g.44145617G>C

NC\_000007.13:g.44185216G>C

CM000669.1:g.44185216G>C

NC\_000007.12:g.44151741G>C

NG\_008847.1:g.48807C>G

NG\_008847.2:g.57554C>G

ENST00000395796.8:c.\*1131C>G

ENST00000616242.5:c.\*253C>G

ENST00000683378.1:n.359C>G

ENST00000336642.9:c.167C>G

ENST00000345378.7:c.1136C>G

ENST00000403799.8:c.1133C>G

ENST00000671824.1:c.1196C>G

ENST00000672743.1:n.145C>G

ENST00000673284.1:c.1133C>G

ENST00000336642.8:c.185C>G

ENST00000345378.6:c.1136C>G

ENST00000395796.7:c.1130C>G

ENST00000403799.7:c.1133C>G

ENST00000437084.1:c.1082C>G

ENST00000459642.1:n.513C>G

ENST00000616242.4:c.1130C>G

NM\_000162.3:c.1133C>G

NM\_033507.1:c.1136C>G

NM\_033508.1:c.1130C>G

NM\_000162.4:c.1133C>G

NM\_001354800.1:c.1133C>G

NM\_001354801.1:c.122C>G

NM\_001354802.1:c.-8C>G

NM\_001354803.1:c.167C>G

NM\_033507.2:c.1136C>G

NM\_033508.2:c.1130C>G

NM\_033507.3:c.1136C>G

NM\_033508.3:c.1130C>G

Likely Pathogenic

Met criteria codes 4

- PP2
- PP3
- PM5\_Strong
- PM2\_Supporting

Not Met criteria codes 3

- PS4
- PP4
- PM1

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 1.2.0*
- [↗](#) **Criteria Specification Approval History**
- [↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1133C>G variant in the glucokinase gene, GCK, causes an amino acid change of alanine to glycine at codon 378 (p.(Ala378Gly)) of NM\_000162.5. This variant has an incomputable Popmax filtering allele frequency in gnomAD 2.1.1 due to only one copy being present, below the PM2\_Supporting threshold of Popmax filtering allele frequency  $\leq 0.000003$  in European Non-Finnish population AND  $\leq 2$  copies observed in ENF AND  $\leq 1$  copy in any other founder or non-founder population (PM2\_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.901, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Additionally, GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). The c.1133C>T, p.(Ala378Val) and c.1132G>A, p.(Ala378Thr) variants have been interpreted as pathogenic by the ClinGen MDEP (PM5\_Strong). This variant was identified in two unrelated individuals with a diabetes; however, this number does not meet the MDEP cutoff for PS4\_Moderate (internal lab contributors). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors). In summary, c.1133C>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 1.2.0, approved 6/7/2023): PM2\_Supporting, PP2, PP3, PM5\_Strong.

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 0.901 which is greater than the MDEP VCEP threshold of 0.70 (PP3).                                                                                                                                                                                                          |
| PM5_Strong     |  |  | The c.1133C>T, p.(Ala378Val) and c.1132G>A, p.(Ala378Thr) variants have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong).                                                                                                                                                                                                                                 |
| PM2_Supporting |  |  | This variant has an incomputable Popmax filtering allele frequency in gnomAD 2.1.1 due to only one copy being present, below the PM2_Supporting threshold of Popmax filtering allele frequency $\leq 0.000003$ in European Non-Finnish population AND $\leq 2$ copies observed in ENF AND $\leq 1$ copy in any other founder or non-founder population (PM2_Supporting). |

Not Met criteria codes

|     |                                                                                   |                                                                                   |                                                                                                                                                                           |
|-----|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PS4 |  |  | This variant was identified in two unrelated individuals with a diabetes; however this number does not meet the MDEP cutoff for PS4_Moderate (internal lab contributors). |
| PP4 |  |  | This variant was identified in an individual with diabetes, however the MODY probability is unable to be calculated due to age of diagnosis over 35.                      |
| PM1 |  |  | Variant is not within a glucose or Mg2+/ATP binding site.                                                                                                                 |

Curation History 

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