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.209G>C

Version: 1.1

CA367398617

2574162 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 23de61da-8a13-4720-89af-873cf375a486
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HGVS expressions

NM_001354803.2:c.209G>C
NC_000007.14:g.44145575C>G
CM000669.2:g.44145575C>G
NC_000007.13:g.44185174C>G
CM000669.1:g.44185174C>G
NC_000007.12:g.44151699C>G
NG_008847.1:g.48849G>C
NG_008847.2:g.57596G>C
ENST00000395796.8:c.*1173G>C
ENST00000616242.5:c.*295G>C
ENST00000683378.1:n.401G>C
ENST00000336642.9:c.209G>C
ENST00000345378.7:c.1178G>C
ENST00000403799.8:c.1175G>C
ENST00000671824.1:c.1238G>C
ENST00000672743.1:n.187G>C
ENST00000673284.1:c.1175G>C
ENST00000336642.8:c.227G>C
ENST00000345378.6:c.1178G>C
ENST00000395796.7:c.1172G>C
ENST00000403799.7:c.1175G>C
ENST00000437084.1:c.1124G>C
ENST00000459642.1:n.555G>C
ENST00000616242.4:c.1172G>C
NM_000162.3:c.1175G>C
NM_033507.1:c.1178G>C
NM_033508.1:c.1172G>C
NM_000162.4:c.1175G>C
NM_001354800.1:c.1175G>C
NM_001354801.1:c.164G>C
NM_001354802.1:c.35G>C
NM_001354803.1:c.209G>C
NM_033507.2:c.1178G>C
NM_033508.2:c.1172G>C
NM_000162.5:c.1175G>C
NM_033507.3:c.1178G>C
NM_033508.3:c.1172G>C

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PM5_Strong PP4_Moderate PM2_Supporting

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 3.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1175G>C variant in the glucokinase gene, GCK, causes an amino acid change of alanine to proline at codon 392 (p.(Arg392Pro)) of NM_000162.5. 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). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.909, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Two other missense variants at the same amino acid position, c.1174C>T p.(Arg392Cys) and c.1175G>T p.(Arg392Leu), have been classified as pathogenic by the ClinGen MDEP (PM5_Strong). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L, HbA1c 5.6 - 7.6%, OGTT increment < 3 mmol/L, and 3 generation family history of diabetes/hyperglycemia) (PP4_Moderate; internal lab contributors). This variant was identified in two unrelated individuals with a clinical picture consistent with monogenic diabetes; however, PS4_Moderate cannot be applied because this number is below the MDEP threshold (PMID: 23624530, internal lab contributors). In summary, this variant meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 3.0.0, approved 7/23/2025): PP2, PP3, PM2_Supporting, PP4_Moderate, PM5_Strong.

Met criteria codes

PP2	✔	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).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.909, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PM5_Strong	✔	Two other missense variants at the same amino acid position, c.1174C>T p.(Arg392Cys) and c.1175G>T p.(Arg392Leu), have been classified as pathogenic by the ClinGen MDEP (PM5_Strong).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L, HbA1c 5.6 - 7.6%, OGTT increment < 3 mmol/L, and 3 generation family history of diabetes/hyperglycemia) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in two unrelated individuals with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold (PMID 23624530, internal lab contributors)

Curation History

Showing 1 to 2 of 2 rows

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