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Variant: NM_001354803.2:c.223C>G

Version: 2.1

CA367398536

2578359 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5196b25c-61aa-49ee-9505-ba8e4e4a0b36
Approved on: 2026/5/6
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HGVS expressions

NM_001354803.2:c.223C>G
NC_000007.14:g.44145561G>C
CM000669.2:g.44145561G>C
NC_000007.13:g.44185160G>C
CM000669.1:g.44185160G>C
NC_000007.12:g.44151685G>C
NG_008847.1:g.48863C>G
NG_008847.2:g.57610C>G
ENST00000395796.8:c.*1187C>G
ENST00000616242.5:c.*309C>G
ENST00000683378.1:n.415C>G
ENST00000336642.9:c.223C>G
ENST00000345378.7:c.1192C>G
ENST00000403799.8:c.1189C>G
ENST00000671824.1:c.1252C>G
ENST00000672743.1:n.201C>G
ENST00000673284.1:c.1189C>G
ENST00000336642.8:c.241C>G
ENST00000345378.6:c.1192C>G
ENST00000395796.7:c.1186C>G
ENST00000403799.7:c.1189C>G
ENST00000437084.1:c.1138C>G
ENST00000459642.1:n.569C>G
ENST00000616242.4:c.1186C>G
NM_000162.3:c.1189C>G
NM_033507.1:c.1192C>G
NM_033508.1:c.1186C>G
NM_000162.4:c.1189C>G
NM_001354800.1:c.1189C>G
NM_001354801.1:c.178C>G
NM_001354802.1:c.49C>G
NM_001354803.1:c.223C>G
NM_033507.2:c.1192C>G
NM_033508.2:c.1186C>G
NM_000162.5:c.1189C>G
NM_033507.3:c.1192C>G
NM_033508.3:c.1186C>G

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP2 PP3 PM5 PP4_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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1189C>G variant in the glucokinase gene, GCK, causes an amino acid change of arginine to glycine at codon 397 (p.(Arg397Gly)) 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 0.817, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and three generation, dominant family history of hyperglycemia) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes with two informative meioses in a single family, however this does not meet the thresholds for PP1 set by the ClinGen MDEP VCEP (internal lab contributor). Another missense variant at the same residue, c.1190G>T p.Arg397Leu, has been interpreted as pathogenic by the ClinGen MDEP VCEP and p.Arg397Gly has a greater Grantham distance (PM5). In summary, c.1189C>G 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 3.1.0, approved 10/10/2025): PM5, PP2, PP3, PP4_Moderate, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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 0.817, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PM5	✔	Another missense variant, c.1190G>T p.Arg397Leu has been interpreted as pathogenic by the ClinGen MDEP VCEP and p.Arg397Gly has a greater Grantham distance (PM5).
PP4_Moderate	✔	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% and three generation, dominant family history of hyperglycemia) (PP4_Moderate; internal lab contributors).

Not Met criteria codes

PP1	✖	This variant segregated with disease with two informative meioses in a single family with diabetes, however this does not meet the thresholds for PP1 set by the ClinGen MDEP VCEP (PMID: 27236918, internal lab contributor).
PS4	✖	This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).

Curation History

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