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Variant: NM_001354803.2:c.152G>C

Version: 1.0

CA4239428

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: ddd7c361-8fce-47a0-a83b-6edc0ee0f8b9
Approved on: 2026/4/17
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HGVS expressions

NM_001354803.2:c.152G>C
NC_000007.14:g.44145632C>G
CM000669.2:g.44145632C>G
NC_000007.13:g.44185231C>G
CM000669.1:g.44185231C>G
NC_000007.12:g.44151756C>G
NG_008847.1:g.48792G>C
NG_008847.2:g.57539G>C
ENST00000395796.8:c.*1116G>C
ENST00000616242.5:c.*238G>C
ENST00000683378.1:n.344G>C
ENST00000336642.9:c.152G>C
ENST00000345378.7:c.1121G>C
ENST00000403799.8:c.1118G>C
ENST00000671824.1:c.1181G>C
ENST00000672743.1:n.130G>C
ENST00000673284.1:c.1118G>C
ENST00000336642.8:c.170G>C
ENST00000345378.6:c.1121G>C
ENST00000395796.7:c.1115G>C
ENST00000403799.7:c.1118G>C
ENST00000437084.1:c.1067G>C
ENST00000459642.1:n.498G>C
ENST00000616242.4:c.1115G>C
NM_000162.3:c.1118G>C
NM_033507.1:c.1121G>C
NM_033508.1:c.1115G>C
NM_000162.4:c.1118G>C
NM_001354800.1:c.1118G>C
NM_001354801.1:c.107G>C
NM_001354802.1:c.-23G>C
NM_001354803.1:c.152G>C
NM_033507.2:c.1121G>C
NM_033508.2:c.1115G>C
NM_000162.5:c.1118G>C
NM_033507.3:c.1121G>C
NM_033508.3:c.1115G>C

Likely Pathogenic

Met criteria codes 4

BS3_Supporting PP2 PP1_Strong PP4_Moderate

Not Met criteria codes 6

PP3 PM5 PM2 BS1 PS4 BP4

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.1118G>C variant in the glucokinase gene, GCK, causes an amino acid change of serine to threonine at codon 373 (p.(Ser373Thr)) 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 has a Grpmax filtering allele frequency of 0.0000143 in gnomAD v4.1.0, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied. This variant has a REVEL score of 0.504, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function. This variant was identified in 8 unrelated individuals with hyperglycemia; however, PS4 cannot be applied because the variant does not meet the PM2_Supporting cutoff (PMID: 36257325, internal lab contributors). At least one of these individuals did have a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and multiple values of mild fasting hyperglycemia) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia with four informative meioses in four families (PP1_Strong; PMID: 34556497, internal lab contributors). Functional studies that met MDEP wild type quality control measures demonstrated that the p.Ser373Thr variant does not result in impaired GCK protein function (RAI >0.5, RSI >0.5, and no impact on GKRP/GKA interaction) (BS3_Supporting; PMID: 41516031). Another missense variant at the same residue, c.1118G>A p.(Ser373Asn), has been classified as a VUS by the ClinGen MDEP; therefore, PM5 will not be applied. In summary, c.1118G>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PP1_Strong, PP2, PP4_Moderate, BS3_Supporting.

Met criteria codes

BS3_Supporting ✔	Functional studies that met MDEP wild type quality control measures demonstrated that the p.Ser373Thr variant does not result in impaired GCK protein function (RAI >0.5, RSI >0.5, and no impact on GKRP/GKA interaction) (BS3_Supporting; PMID: 41516031)
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).
PP1_Strong ✔	This variant segregated with hyperglycemia with four informative meioses in four families (PP1_Strong; PMID: 34556497, internal lab contributors).
PP4_Moderate ✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and multiple values of mild fasting hyperglycemia) (PP4_Moderate; internal lab contributors).

Not Met criteria codes

PP3	✖	This variant has a REVEL score of 0.504, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function.
PM5	✖	Another missense variant, [c.1118G>A p.(Ser373Asn)] has been classified as a VUS by the ClinGen MDEP; therefore, PM5 will not be applied.
PM2	✖	This variant has a Grpmax filtering allele frequency of 0.0000143 in gnomAD v4.1.0, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied.
BS1	✖	This variant has a Grpmax filtering allele frequency of 0.0000143 in gnomAD v4.1.0, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied.
PS4	✖	This variant was identified in 7 unrelated individuals with hyperglycemia; however, PS4 cannot be applied because the variant does not meet the PM2_Supporting cutoff (PMID: 36257325, internal lab contributors).
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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