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_000162.5(GCK):c.1019G>C (p.Ser340Thr)

Version: 1.1

CA367399685

2580863 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 4b9b1b16-1f53-4526-aad5-feb14cb22c67
Approved on: 2025/11/18
Published on: 2025/11/18

HGVS expressions

NM_000162.5:c.1019G>C
NM_000162.5(GCK):c.1019G>C (p.Ser340Thr)
NC_000007.14:g.44146463C>G
CM000669.2:g.44146463C>G
NC_000007.13:g.44186062C>G
CM000669.1:g.44186062C>G
NC_000007.12:g.44152587C>G
NG_008847.1:g.47961G>C
NG_008847.2:g.56708G>C
ENST00000395796.8:c.*1017G>C
ENST00000616242.5:c.*139G>C
ENST00000683378.1:n.245G>C
ENST00000345378.7:c.1022G>C
ENST00000403799.8:c.1019G>C
ENST00000671824.1:c.1082G>C
ENST00000673284.1:c.1019G>C
ENST00000345378.6:c.1022G>C
ENST00000395796.7:c.1016G>C
ENST00000403799.7:c.1019G>C
ENST00000437084.1:c.968G>C
ENST00000473353.1:n.317G>C
ENST00000616242.4:c.1016G>C
NM_000162.3:c.1019G>C
NM_033507.1:c.1022G>C
NM_033508.1:c.1016G>C
NM_000162.4:c.1019G>C
NM_001354800.1:c.1019G>C
NM_001354801.1:c.8+156G>C
NM_033507.2:c.1022G>C
NM_033508.2:c.1016G>C
NM_033507.3:c.1022G>C
NM_033508.3:c.1016G>C

Pathogenic

Met criteria codes 6

PP4_Moderate PP1_Strong PM2_Supporting PS3 PS4_Moderate 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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1019G>C variant in the glucokinase gene, GCK, causes an amino acid change of serine to threonine at codon 340 (p.(Ser340Thr)) of NM_000162.5. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 24804978, 28012402, 34440516, 36257325, internal lab contributors). Furthermore, one of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% in an incidentally identified pediatric individual during routine screening) (PP4_Moderate; PMID: 24804978). This variant segregated with hyperglycemia with four informative meioses in three families (PP1_Strong; PMID: 28012402, 29927023, 34440516). While this variant has a REVEL score of 0.662, which does not meet ClinGen MDEP cutoffs for PP3 or BP4, the computational splicing predictor SpliceAI gives a score of 0.93 for donor loss, predicting that the variant disrupts the donor site of intron 8 (PP3). Additionally, there is evidence from RNA studies that this non-canonical splicing variant results in aberrant splicing, indicating that this variant impacts protein function (PS3; PMID: 40225161). In summary, c.1019G>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS3, PP1_Strong, PS4_Moderate, PP4_Moderate, PM2_Supporting, PP3.

Met criteria codes

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% in an incidentally identified pediatric individual during routine screening) (PP4_Moderate; PMID: 24804978).
PP1_Strong	✔	This variant segregated with hyperglycemia with four informative meioses in three families (PP1_Strong; PMID: 28012402, 29927023, 34440516).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS3	✔	There is evidence from RNA and in silico studies that this non-canonical splicing variant results in aberrant splicing, indicating that this variant impacts protein function (PS3; PMID: 40225161).
PS4_Moderate	✔	This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 24804978, 28012402, 34440516, 36257325, internal lab contributors).
PP3	✔	While this variant has a REVEL score of 0.662, which does not meet ClinGen MDEP cutoffs for PP3 or BP4, the computational splicing predictor SpliceAI gives a score of 0.93 for donor loss, predicting that the variant disrupts the

donor site of intron 8 (PP3).

Curation History

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