Variant: NM_000162.5(GCK):c.951C>G (p.His317Gln)

Version: 1.0

CA367399915

447426 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b7c26c11-f27a-4df9-80c5-6c7875261b2b
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HGVS expressions

NM_000162.5:c.951C>G
NM_000162.5(GCK):c.951C>G (p.His317Gln)
NC_000007.14:g.44146531G>C
CM000669.2:g.44146531G>C
NC_000007.13:g.44186130G>C
CM000669.1:g.44186130G>C
NC_000007.12:g.44152655G>C
NG_008847.1:g.47893C>G
NG_008847.2:g.56640C>G
ENST00000395796.8:c.*949C>G
ENST00000616242.5:c.*71C>G
ENST00000683378.1:n.177C>G
ENST00000345378.7:c.954C>G
ENST00000403799.8:c.951C>G
ENST00000671824.1:c.1014C>G
ENST00000673284.1:c.951C>G
ENST00000345378.6:c.954C>G
ENST00000395796.7:c.948C>G
ENST00000403799.7:c.951C>G
ENST00000437084.1:c.900C>G
ENST00000473353.1:n.249C>G
ENST00000616242.4:c.948C>G
NM_000162.3:c.951C>G
NM_033507.1:c.954C>G
NM_033508.1:c.948C>G
NM_000162.4:c.951C>G
NM_001354800.1:c.951C>G
NM_001354801.1:c.8+88C>G
NM_033507.2:c.954C>G
NM_033508.2:c.948C>G
NM_033507.3:c.954C>G
NM_033508.3:c.948C>G

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PP2 PP3
PP1_Moderate

Not Met criteria codes 4

PS4 PM2 PM1 BS1

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.951C>G variant in the glucokinase gene, GCK, causes an amino acid change of histidine to glutamine at codon 317 (p.(His317Gln)) 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 REVEL score of 0.191, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function. However, the computational splicing predictor SpliceAI gives a score of 0.34 for acceptor gain, indicating that this variant may disrupt GCK splicing (PP3). The Grpmax filtering allele frequency of the c.951C>G variant in gnomAD v4.1.0 is 0.00000803, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied. This variant has been identified in at leat 15 individuals with hyperglycemia; however, PS4 cannot be applied because the variant Grpmax in gnomAD is above the ClinGen MDEP PM2_Supporting cutoff (PMID: 31063852, 36257325, internal lab contributors). At least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (persistent hyperglycemia with multiple documented values (≥ 2) of fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia with three informative meioses in three families (PP1_Moderate; PMID: 31063852; internal lab contributors). In summary, c.951C>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 3.0.0, approved 7/23/2025): PP4_Moderate, PP1_Moderate, PP2, PP3.

Met criteria codes

PP4_Moderate	✓	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (persistent hyperglycemia with multiple documented values (≥ 2) of fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4_Moderate; internal lab contributors).
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 has a REVEL score of 0.191, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function. However, the computational splicing predictor SpliceAI gives a score of 0.34 for acceptor gain, indicating that this variant may disrupt GCK splicing (PP3).
PP1_Moderate	✓	This variant segregated with hyperglycemia with three informative meioses in three families (PP1_Moderate; PMID: 31063852; internal lab contributors).

Not Met criteria codes

PS4	ℹ	✖	This variant has been identified in at least 15 individuals with hyperglycemia; however, PS4 cannot be applied because the variant Grpmax in gnomAD is above the ClinGen MDEP PM2_Supporting cutoff (PMID: 31063852, 36257325, internal lab contributors).
PM2		✖	The Grpmax filtering allele frequency of the c.951C>G variant in gnomAD v4.1.0 is 0.00000803, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied.
PM1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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