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Variant: NM_033508.3:c.167T>C

Version: 2.0

CA367403316

3720746 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 56e055bf-1a82-4b18-bddd-bd74d7f701e4
Approved on: 2025/10/28
Published on: 2025/10/28

HGVS expressions

NM_033508.3:c.167T>C
NC_000007.14:g.44153339A>G
CM000669.2:g.44153339A>G
NC_000007.13:g.44192938A>G
CM000669.1:g.44192938A>G
NC_000007.12:g.44159463A>G
NG_008847.1:g.41085T>C
NG_008847.2:g.49832T>C
ENST00000395796.8:c.*168T>C
ENST00000616242.5:c.170T>C
ENST00000682635.1:n.656T>C
ENST00000345378.7:c.173T>C
ENST00000403799.8:c.170T>C
ENST00000671824.1:c.170T>C
ENST00000673284.1:c.170T>C
ENST00000345378.6:c.173T>C
ENST00000395796.7:c.167T>C
ENST00000403799.7:c.170T>C
ENST00000437084.1:c.170T>C
ENST00000616242.4:c.167T>C
NM_000162.3:c.170T>C
NM_033507.1:c.173T>C
NM_033508.1:c.167T>C
NM_000162.4:c.170T>C
NM_001354800.1:c.170T>C
NM_033507.2:c.173T>C
NM_033508.2:c.167T>C
NM_000162.5:c.170T>C
NM_033507.3:c.173T>C

Likely Pathogenic

Met criteria codes 5

PM5 PP4_Moderate PP2 PP3 PM2_Supporting

Not Met criteria codes 2

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS4 PP1

Evidence Links 0

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.170T>C variant in the glucokinase gene, GCK, causes an amino acid change of methionine to threonine at codon 57 (p.(Met57Thr)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting). 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 is predicted to be deleterious by computational evidence, with a REVEL score of 0.987, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 22035297; internal lab contributors). 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 negative autoantibodies) (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 (PMID: 27236918, internal lab contributors). Another missense variant at the same codon, c.171G>A, p.(Met57Ile), has been interpreted as pathogenic by the ClinGen MDEP, and p.(Met57Thr) has a greater Grantham distance (PM5). In summary, c.170T>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 3.1.1, approved 10/10/2025): PM2_Supporting, PP2, PP3, PP4_Moderate, PM5.

Met criteria codes

PM5	✔	Another missense variant at the same codon, c.171G>A, p.(Met57Ile), has been interpreted as pathogenic by the ClinGen MDEP, and p.(Met57Thr) has a greater Grantham distance (PM5).
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 negative autoantibodies) (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 is predicted to be deleterious by computational evidence, with a REVEL score of 0.987, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 22035297; internal lab contributors).
PP1	✖	

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 (PMID: 27236918, internal lab contributors).

Curation History

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