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_033508.3:c.167T>G

Version: 1.0

CA367403318

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 80810179-5dcf-4d2d-a313-2582a98bd120
Approved on: 2024/10/31
Published on: 2025/2/28

HGVS expressions

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

Likely Pathogenic

Met criteria codes 6

PM3_Supporting PP2 PP3 PP4 PM5 PM2_Supporting

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 1.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.170T>G variant in the glucokinase gene, GCK, causes an amino acid change of methionine to arginine at codon 57 (p.(Met57Arg)) 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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors). Additionally, it has been detected in the homozygous state in one individual with neonatal diabetes (PM3_Supporting, PMID: 38970407). Another missense variant at the same codon, c.171G>A, p.(Met57Ile), has been interpreted as pathogenic by the ClinGen MDEP, and p.(Met57Arg) has a greater Grantham distance (PM5). In summary, c.170T>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 1.3.0, approved 8/11/2023): PM2_Supporting, PP2, PP3, PP4, PM3_Supporting, PM5).

Met criteria codes

PM3_Supporting	✔	This variant has been detected in the homozygous state in one individual with neonatal diabetes (PM3_Supporting, PMID: 38970407).
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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4	✔	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%) (PP4; internal lab contributors).
PM5	✔	Another missense variant at the same codon, c.171G>A, p.(Met57Ile), has been interpreted as pathogenic by the ClinGen MDEP, and p.(Met57Arg) has a greater Grantham distance (PM5).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.