

Variant: *NM_000162.5(GCK):c.1099G>A (p.Val367Met)*

Version: 1.0

CA16605802 [↗](#)

381598 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

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HGVS expressions

NM_000162.5(GCK):c.1099G>A (p.Val367Met)

NM_000162.5:c.1099G>A

NC_000007.14:g.44145651C>T

CM000669.2:g.44145651C>T

NC_000007.13:g.44185250C>T

CM000669.1:g.44185250C>T

NC_000007.12:g.44151775C>T

NG_008847.1:g.48773G>A

NG_008847.2:g.57520G>A

ENST00000395796.8:c.*1097G>A

ENST00000616242.5:c.*219G>A

ENST00000683378.1:n.325G>A

ENST00000336642.9:c.133G>A

ENST00000345378.7:c.1102G>A

ENST00000403799.8:c.1099G>A

ENST00000671824.1:c.1162G>A

ENST00000672743.1:n.111G>A

ENST00000673284.1:c.1099G>A

ENST00000336642.8:c.151G>A

ENST00000345378.6:c.1102G>A

ENST00000395796.7:c.1096G>A

ENST00000403799.7:c.1099G>A

ENST00000437084.1:c.1048G>A

ENST00000459642.1:n.479G>A

ENST00000473353.1:n.397G>A

ENST00000616242.4:c.1096G>A

NM_000162.3:c.1099G>A

NM_033507.1:c.1102G>A

NM_033508.1:c.1096G>A

NM_000162.4:c.1099G>A

NM_001354800.1:c.1099G>A

NM_001354801.1:c.88G>A

NM_001354802.1:c.-42G>A

NM_001354803.1:c.133G>A

NM_033507.2:c.1102G>A

NM_033508.2:c.1096G>A

NM_033507.3:c.1102G>A

NM_033508.3:c.1096G>A
NM_001354803.2:c.133G>A

Pathogenic

Met criteria codes 6

PP1_Strong PP2 PP3 PP4 PS4
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 1.0.0
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1099G>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to methionine at codon 367 (p.(Val367Met)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.929, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 7 unrelated individuals with diabetes/hyperglycemia (PS4; PMID 27256595, 31968686, 9049484, internal lab contributors). This variant segregated with diabetes with 4 informative meioses in 3 families with diabetes/hyperglycemia (PP1_Strong; PMID 27256595, 9049484, internal lab contributors). 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; PMID 27256595). In summary, this variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2.0, approved 6/7/2023): PP2, PP3, PM2_Supporting, PS4, PP4, PP1_Strong.

Met criteria codes

PP1_Strong		✓	This variant segregated with diabetes with 4 informative meioses in 3 families with diabetes (PP1_Strong; PMID 27256595, 9049484, 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 0.929, 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; PMID 27256595).
PS4		✓	This variant was identified in 7 unrelated individuals with diabetes/hyperglycemia (PS4; PMID 27256595, 31968686, 9049484, internal lab contributors)

PM2_Supporting

This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Curation History

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