

Variant: NM_000162.5(GCK):c.184G>A (p.Val62Met)

Version: 1.0

CA16618472 [↗](#)

419624 (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.184G>A (p.Val62Met)

NM_000162.5:c.184G>A

NC_000007.14:g.44153325C>T

CM000669.2:g.44153325C>T

NC_000007.13:g.44192924C>T

CM000669.1:g.44192924C>T

NC_000007.12:g.44159449C>T

NG_008847.1:g.41099G>A

NG_008847.2:g.49846G>A

ENST00000395796.8:c.*182G>A

ENST00000616242.5:c.184G>A

ENST00000682635.1:n.670G>A

ENST00000345378.7:c.187G>A

ENST00000403799.8:c.184G>A

ENST00000671824.1:c.184G>A

ENST00000673284.1:c.184G>A

ENST00000345378.6:c.187G>A

ENST00000395796.7:c.181G>A

ENST00000403799.7:c.184G>A

ENST00000437084.1:c.184G>A

ENST00000616242.4:c.181G>A

NM_000162.3:c.184G>A

NM_033507.1:c.187G>A

NM_033508.1:c.181G>A

NM_000162.4:c.184G>A

NM_001354800.1:c.184G>A

NM_033507.2:c.187G>A

NM_033508.2:c.181G>A

NM_033507.3:c.187G>A

NM_033508.3:c.181G>A

Pathogenic

Met criteria codes 7

PS3_Supporting

PP4_Moderate

PP2

PP3

PP1_Strong

PS4_Moderate

PM2_Supporting

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 1.2.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.184G>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to methionine at codon 62 (p.(Val62Met)) 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 is also predicted to be deleterious by computational evidence, with a REVEL score of 0.972, which is greater than the MDEP VCEP threshold of 0.70 (PP3). While p.Val62Met did not have reduction in enzyme activity or stability, its activity was unresponsive to GKRP (PS3_Supporting; PMID 15677479). This variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in six unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID:15677479, PMID: 28726111, ClinVar ID: 419624, internal lab contributors). At least two of these individuals had a clinical history highly specific for for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L) (PP4_Moderate; PMID:15677479). This variant segregated with diabetes, with six informative meioses in two families with MODY (PP1_Strong; PMID: 15677479). In summary, c.184G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_strong, PP4_moderate, PS4_moderate, PP2, PP3, PM2_Supporting, PS3_Supporting.

Met criteria codes

PS3_Supporting			While p.Val62Met did not have reduction in enzyme activity or stability, its activity was unresponsive to GKRP (PS3_Supporting; PMID 15677479).
PP4_Moderate			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% and OGTT increment < 3 mmol/L) (PP4_Moderate; PMID:15677479).
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 0.972, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong			This variant segregated with diabetes, with six informative meioses in two families with MODY (PP1_Strong; PMID: 15677479).
PS4_Moderate			This variant was identified in six unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID:15677479, PMID: 28726111, ClinVar ID: 419624, internal lab contributors).

PM2_Supporting ⓘ



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

Curation History ↗

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