

Variant: *NM_000162.5(GCK):c.98T>C (p.Val33Ala)*

Version: 1.0

CA367403604 [↗](#)

585930 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 36f8d790-f31d-4409-b22e-8ef6101888b9

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HGVS expressions

NM_000162.5:c.98T>C

NM_000162.5(GCK):c.98T>C (p.Val33Ala)

NC_000007.14:g.44153411A>G

CM000669.2:g.44153411A>G

NC_000007.13:g.44193010A>G

CM000669.1:g.44193010A>G

NC_000007.12:g.44159535A>G

NG_008847.1:g.41013T>C

NG_008847.2:g.49760T>C

ENST00000395796.8:c.*96T>C

ENST00000616242.5:c.98T>C

ENST00000682635.1:n.584T>C

ENST00000345378.7:c.101T>C

ENST00000403799.8:c.98T>C

ENST00000671824.1:c.98T>C

ENST00000673284.1:c.98T>C

ENST00000345378.6:c.101T>C

ENST00000395796.7:c.95T>C

ENST00000403799.7:c.98T>C

ENST00000437084.1:c.98T>C

ENST00000476008.1:n.533T>C

ENST00000616242.4:c.95T>C

NM_000162.3:c.98T>C

NM_033507.1:c.101T>C

NM_033508.1:c.95T>C

NM_000162.4:c.98T>C

NM_001354800.1:c.98T>C

NM_033507.2:c.101T>C

NM_033508.2:c.95T>C

NM_033507.3:c.101T>C

NM_033508.3:c.95T>C

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PP2

PP3

PS4

PM2_Supporting

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Not Met criteria codes 3

PS3 PM1 PM5

Evidence Links 0

Criteria Specification Information

[Criteria Specification:](#) *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 2.0.0*

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.98T>C variant in the glucokinase gene, GCK, causes an amino acid change of valine to alanine at codon 33 (p.(Val33Ala)) of NM_000162.5. This variant was identified in at least 17 unrelated individuals with hyperglycemia (PS4; PMID: 22332836, 26641800, 36257325 internal lab contributors). This variant is absent from gnomAD v4.1.0 (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 0.929, 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-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative (PP4_Moderate; internal lab contributors). The relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, and thermostability was not evaluated; therefore PS3 was not applied (PMID: 28842611). Additional missense variants at the same codon, c.98T>A p.(Val33Glu) and c.98T>G p.(Val33Gly) have been classified as a VUS by the ClinGen MDEP; therefore, PM5 will not be applied. In summary, c.98T>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 2.0.0, approved 2/17/2025): PS4, PM2_Supporting, PP2, PP3, PP4_Moderate.

Met criteria codes

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 antibody negative (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 0.929, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4			This variant was identified in at least 17 unrelated individuals with hyperglycemia (PS4; PMID: 22332836 (10), 26641800 (2), 36257325 (1), internal lab contributors).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS3			The relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, and thermostability was not evaluated; therefore PS3 was not applied (PMID: 28842611).
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PM1			This variant does not reside in an amino acid that directly binds glucose or ATP, which are defined as critical for the GCK protein's function by the ClinGen MDEP.
PM5			Additional missense variants, c.98T>A p.(Val33Glu) and c.98T>G p.(Val33Gly) have been classified as a VUS by the ClinGen MDEP; therefore, PM5 will not be applied.

Curation History 		
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