

Variant: NM_001354803.2:c.155T>A

Version: 1.0

CA367398869 [↗](#)

2578348 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 69e32040-c6a1-42ad-a581-319eed5ecfac

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HGVS expressions

NM_001354803.2:c.155T>A

NC_000007.14:g.44145629A>T

CM000669.2:g.44145629A>T

NC_000007.13:g.44185228A>T

CM000669.1:g.44185228A>T

NC_000007.12:g.44151753A>T

NG_008847.1:g.48795T>A

NG_008847.2:g.57542T>A

ENST00000395796.8:c.*1119T>A

ENST00000616242.5:c.*241T>A

ENST00000683378.1:n.347T>A

ENST00000336642.9:c.155T>A

ENST00000345378.7:c.1124T>A

ENST00000403799.8:c.1121T>A

ENST00000671824.1:c.1184T>A

ENST00000672743.1:n.133T>A

ENST00000673284.1:c.1121T>A

ENST00000336642.8:c.173T>A

ENST00000345378.6:c.1124T>A

ENST00000395796.7:c.1118T>A

ENST00000403799.7:c.1121T>A

ENST00000437084.1:c.1070T>A

ENST00000459642.1:n.501T>A

ENST00000616242.4:c.1118T>A

NM_000162.3:c.1121T>A

NM_033507.1:c.1124T>A

NM_033508.1:c.1118T>A

NM_000162.4:c.1121T>A

NM_001354800.1:c.1121T>A

NM_001354801.1:c.110T>A

NM_001354802.1:c.-20T>A

NM_001354803.1:c.155T>A

NM_033507.2:c.1124T>A

NM_033508.2:c.1118T>A

NM_000162.5:c.1121T>A

NM_033507.3:c.1124T>A

NM_033508.3:c.1118T>A

Likely Pathogenic

Met criteria codes 5

PM2_Supporting

PP2

PP3

PM5_Supporting

PP4_Moderate

Not Met criteria codes 1

PS4

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.1121T>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to glutamic acid at codon 374 (p.(Val374Glu)) 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 0.968, 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 an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). Another missense variant, c.1120G>A p.(Val374Met), has been classified as likely pathogenic by the ClinGen MDEP VCEP (PM5_Supporting). This variant was identified in two unrelated individuals with hypglycemia; however, this number does not meet the MDEP cutoff for PS4_Moderate (Solano et al. 2019. Rev Esp Endocrinol Pediatr 10(2):69-73, internal lab contributors). In summary, this variant meets the criteria to be classified as likely 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, PP4_Moderate, PM5_Supporting .

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
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 0.968, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5_Supporting			Another missense variant, c.1120G>A p.(Val374Met), has been classified as likely pathogenic by the ClinGen MDEP VCEP (PM5_Supporting).
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 negative antibodies) (PP4_Moderate; internal lab contributors).

Not Met criteria codes

PS4			This variant was identified in two unrelated individuals with hyperglycemia; however, this number does not meet the MDEP cutoff for PS4_Moderate (Solano et al. 2019. Rev Esp Endocrinol Pediatr 10(2):69-73, internal lab contributors).
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Curation History 

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