

Variant: NM_000162.5(GCK):c.1055T>C (p.Leu352Pro)

Version: 1.0

CA367399230 [↗](#)

3893306 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))
Condition: monogenic diabetes ([MONDO:0015967](#))
Inheritance Mode: Semidominant inheritance
UUID: 53eeda59-425b-4b61-bd9f-b24955545514
Approved on: 2025/7/18
Published on: 2025/7/25

HGVS expressions

NM_000162.5:c.1055T>C
NM_000162.5(GCK):c.1055T>C (p.Leu352Pro)
NC_000007.14:g.44145695A>G
CM000669.2:g.44145695A>G
NC_000007.13:g.44185294A>G
CM000669.1:g.44185294A>G
NC_000007.12:g.44151819A>G
NG_008847.1:g.48729T>C
NG_008847.2:g.57476T>C
ENST00000395796.8:c.*1053T>C
ENST00000616242.5:c.*175T>C
ENST00000683378.1:n.281T>C
ENST00000336642.9:c.89T>C
ENST00000345378.7:c.1058T>C
ENST00000403799.8:c.1055T>C
ENST00000671824.1:c.1118T>C
ENST00000672743.1:n.67T>C
ENST00000673284.1:c.1055T>C
ENST00000336642.8:c.107T>C
ENST00000345378.6:c.1058T>C
ENST00000395796.7:c.1052T>C
ENST00000403799.7:c.1055T>C
ENST00000437084.1:c.1004T>C
ENST00000459642.1:n.435T>C
ENST00000473353.1:n.353T>C
ENST00000616242.4:c.1052T>C
NM_000162.3:c.1055T>C
NM_033507.1:c.1058T>C
NM_033508.1:c.1052T>C
NM_000162.4:c.1055T>C
NM_001354800.1:c.1055T>C
NM_001354801.1:c.44T>C
NM_001354802.1:c.-86T>C
NM_001354803.1:c.89T>C
NM_033507.2:c.1058T>C
NM_033508.2:c.1052T>C
NM_033507.3:c.1058T>C

NM_033508.3:c.1052T>C
NM_001354803.2:c.89T>C

Likely Pathogenic

Met criteria codes 6

PM2_Supporting PS4_Moderate
PS2_Moderate PP4_Moderate PP2
PP3

Not Met criteria codes 2

PP1 PM1

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 2.0.0
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1055T>C variant in the glucokinase gene, GCK, causes an amino acid change of leucine to proline at codon 352 (p.(Leu352Pro)) 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 absent from gnomAD v4.1.0 genomes (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.99, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 29056535, Sertedaki et al. 2004 Horm Res 62(suppl 2),147, P3-532; internal lab contributors). Additionally, two of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors), and in one of the individuals the variant was identified as a de novo occurrence with unconfirmed parental relationships (PS2_Moderate; internal lab contributors). This variant segregated with diabetes with one informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors). In summary, c.1055T>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): PP2, PP3, PM2_Supporting, PP4_Moderate, PS2_Moderate, PS4_Moderate.

Met criteria codes

PM2_Supporting		✓	This variant is absent from gnomAD v4.1.0 genomes (PM2_Supporting).
PS4_Moderate		✓	This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: PMID: 29056535, Sertedaki et al. 2004 Horm Res 62(suppl 2),147, P3-532; internal lab contributors).
PS2_Moderate		✓	This variant was identified as a de novo occurrence with unconfirmed parental relationships in an individual with a clinical picture consistent with GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PS2_Moderate; internal lab contributors).
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 negative antibodies) (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 0.99, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
Not Met criteria codes			
PP1			This variant segregated with diabetes with one informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, binternal lab contributors).
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 			
			
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