

Variant: NM_000162.5(GCK):c.1364T>A (p.Val455Glu)

Version: 1.0

CA4239373 [↗](#)

585916 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 918d7c2e-8ace-4687-b916-dd1b836593c5

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HGVS expressions

NM_000162.5:c.1364T>A

NM_000162.5(GCK):c.1364T>A (p.Val455Glu)

NC_000007.14:g.44145170A>T

CM000669.2:g.44145170A>T

NC_000007.13:g.44184769A>T

CM000669.1:g.44184769A>T

NC_000007.12:g.44151294A>T

NG_008847.1:g.49254T>A

NG_008847.2:g.58001T>A

ENST00000395796.8:c.*1362T>A

ENST00000616242.5:c.*484T>A

ENST00000683378.1:n.590T>A

ENST00000336642.9:c.398T>A

ENST00000345378.7:c.1367T>A

ENST00000403799.8:c.1364T>A

ENST00000671824.1:c.1427T>A

ENST00000672743.1:n.376T>A

ENST00000673284.1:c.1364T>A

ENST00000336642.8:c.416T>A

ENST00000345378.6:c.1367T>A

ENST00000395796.7:c.1361T>A

ENST00000403799.7:c.1364T>A

ENST00000437084.1:c.1313T>A

ENST00000459642.1:n.744T>A

ENST00000616242.4:c.1361T>A

NM_000162.3:c.1364T>A

NM_033507.1:c.1367T>A

NM_033508.1:c.1361T>A

NM_000162.4:c.1364T>A

NM_001354800.1:c.1364T>A

NM_001354801.1:c.353T>A

NM_001354802.1:c.224T>A

NM_001354803.1:c.398T>A

NM_033507.2:c.1367T>A

NM_033508.2:c.1361T>A

NM_033507.3:c.1367T>A

NM_033508.3:c.1361T>A

Likely Pathogenic

Met criteria codes 7

PP1_Strong PS4 PP4_Moderate
PP2 PP3 PS3_Supporting BS1

Not Met criteria codes 2

PM1 PM2

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 3.1.0
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1364T>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to glutamic acid at codon 455 (p.(Val455Glu)) 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 predicted to be deleterious by computational evidence, with a REVEL score of 0.928, which is greater than the MDEP VCEP threshold of 0.70 (PP3). An enzyme kinetic study was performed in which the WT parameters kcat and S0.5 were within MDEP quality control range, but the ATPkm exceeded the range. The relative MT:WT kcat/S0.5 ratio was 0.22, which is within the MDEP cutoff for PS3_Supporting (PS3_Supporting: PMID:184811947 and Personal Communication, A. Gloyn). This variant has a Grpmax filtering allele frequency of 0.00005031 in gnomAD v4.1, which exceeds the cutoff of 0.00004 for BS1 (BS1). This variant was identified in at least 28 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes, but PS4 cannot be applied on this basis because the variant does not meet the MDEP PM2_Supporting cutoff (PMIDs: 25555462, 18481947, internal lab contributors). However, the variant was associated with type 2 diabetes with an odds ratio of 8.7 (p = 0.00002) in a meta-analysis and with elevated glucose (beta = 0.781 mmol/L, p = 0.00008) and HbA1c (beta = 5.11 mmol/L, p = 0.00000074) in the UK Biobank. Given that an actual case-control study of hyperglycemia meets the original ACMGv3 cutoff for PS4 (OR > 5), this criterion was applied (PS4; PMID: 39379762). Notably, consistent with its higher frequency, the same study showed a smaller effect size than classical GCK-MODY variants in aggregate (e.g., diabetes OR = 360, p = 6 x 10-19), and therefore the p.Val455Glu variant was designated as a variant of intermediate penetrance for T2D (PMID: 39379762). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody-negative) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia, with ten informative meioses in six families (PP1_Strong; internal lab contributors). In summary, c.1364T>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4, PP1_Strong, PP4_Moderate, PP2, PP3, PS3_Supporting, BS1. Importantly, while the variant appears to have lower effect size than typical P/LP GCK variants, MDEP recommends reporting it as likely pathogenic given that identifying it in an individual with otherwise unexplained, mild hyperglycemia indicates a higher glycemic setpoint for insulin release that may neither require nor respond to treatment.

Met criteria codes

PP1_Strong



This variant segregated with hyperglycemia, with ten informative meioses in six families (PP1_Strong; internal lab contributors).

PS4



This variant was identified in at least 28 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes, but PS4 cannot be applied on this basis because the variant does not meet the MDEP PM2_Supporting cutoff (PMIDs: 25555462, 18481947, internal lab contributors). However, the variant was

associated with type 2 diabetes with an odds ratio of 8.7 (p = 0.00002) in a meta-analysis and with elevated fasting glucose (beta = 0.781 mmol/L, p = 0.00008) and HbA1c (beta = 5.11 mmol/L, p = 0.00000074). Given that an actual case-control study of hyperglycemia meets the original ACMGv3 cutoff for PS4 (OR > 5), PS4 was applied (PS4).

PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 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 0.928, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS3_Supporting			An enzyme kinetic study was performed in which the WT parameters kcat and S0.5 were within MDEP quality control range, but the ATPkm exceeded the range. The relative MT:WT kcat:S0.5 ratio was 0.22, which was within the MDEP cutoff for PS3_Supporting (PS3_Supporting: PMID:184811947 and Personal Communication, A. Gloyn).
BS1			The Popmax filtering allele frequency of the c.1364T>A variant in gnomAD v4.1 0.00005031, which exceeds the cutoff of 0.00004 for BS1 (BS1).

Not Met criteria codes

PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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