

Variant: NM_000162.5(GCK):c.1268T>C (p.Phe423Ser)

CA367397256 [↗](#)

447389 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: f8250e2f-732b-49b2-bf40-760a0fc74a9c

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Version: 1.0

HGVS expressions

NM_000162.5(GCK):c.1268T>C (p.Phe423Ser)

NM_000162.5:c.1268T>C

NC_000007.14:g.44145266A>G

CM000669.2:g.44145266A>G

NC_000007.13:g.44184865A>G

CM000669.1:g.44184865A>G

NC_000007.12:g.44151390A>G

NG_008847.1:g.49158T>C

NG_008847.2:g.57905T>C

ENST00000395796.8:c.*1266T>C

ENST00000616242.5:c.*388T>C

ENST00000683378.1:n.494T>C

ENST00000336642.9:c.302T>C

ENST00000345378.7:c.1271T>C

ENST00000403799.8:c.1268T>C

ENST00000671824.1:c.1331T>C

ENST00000672743.1:n.280T>C

ENST00000673284.1:c.1268T>C

ENST00000336642.8:c.320T>C

ENST00000345378.6:c.1271T>C

ENST00000395796.7:c.1265T>C

ENST00000403799.7:c.1268T>C

ENST00000437084.1:c.1217T>C

ENST00000459642.1:n.648T>C

ENST00000616242.4:c.1265T>C

NM_000162.3:c.1268T>C

NM_033507.1:c.1271T>C

NM_033508.1:c.1265T>C

NM_000162.4:c.1268T>C

NM_001354800.1:c.1268T>C

NM_001354801.1:c.257T>C

NM_001354802.1:c.128T>C

NM_001354803.1:c.302T>C

NM_033507.2:c.1271T>C

NM_033508.2:c.1265T>C

NM_033507.3:c.1271T>C

NM_033508.3:c.1265T>C

Uncertain Significance

Met criteria codes 4

PP2 PP3 PM5 PM2_Supporting

Not Met criteria codes 5

PS4 BA1 PP4 BS1 BP4

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 1.3.0*
-
- [↗](#)
- Criteria Specification Approval History**
-
- [↗](#)
- Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1268T>C variant in the glucokinase gene, GCK, causes an amino acid change of phenylalanine to serine at codon 423 (p.(Phe423Ser)) 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 0.973, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Another missense variant, c.1268T>A, p.Phe423Tyr has been interpreted as pathogenic by the ClinGen MDEP, and p.Phe423Ser has a greater Grantham distance (PM5). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (PMIDs: 25555642, internal lab contributors). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 25555642, internal lab contributors). In summary, c.1268T>C meets the criteria to be classified as a variant of uncertain significance for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM2_supporting, PP2, PP3, PM5.

Met criteria codes

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 0.973, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5		✓	Another missense variant, c.1268T>A, p.Phe423Tyr has been interpreted as pathogenic by the ClinGen MDEP, and p.Phe423Ser has a greater Grantham distance (PM5). NM_000162.5(GCK): was classified as pathogenic and Phe-Tyr Grantham distance =22, lower than Phe-Ser Grantham distance 155.
PM2_Supporting		✓	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). absent from gnomAD v4.0.0

Not Met criteria codes

PS4			This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 25555642, internal lab contributors).
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (PMIDs: 25555642, internal lab contributors).
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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