The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000162.5(GCK):c.1264C>T (p.Arg422Trp)

Version: 1.0

CA367397271

1700675 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 6b0135a9-3845-4df1-a393-598775a2b89c
Approved on: Mon, 21 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000162.5(GCK):c.1264C>T (p.Arg422Trp)
NM_000162.5:c.1264C>T
NC_000007.14:g.44145270G>A
CM000669.2:g.44145270G>A
NC_000007.13:g.44184869G>A
CM000669.1:g.44184869G>A
NC_000007.12:g.44151394G>A
NG_008847.1:g.49154C>T
NG_008847.2:g.57901C>T
ENST00000395796.8:c.*1262C>T
ENST00000616242.5:c.*384C>T
ENST00000683378.1:n.490C>T
ENST00000336642.9:c.298C>T
ENST00000345378.7:c.1267C>T
ENST00000403799.8:c.1264C>T
ENST00000671824.1:c.1327C>T
ENST00000672743.1:n.276C>T
ENST00000673284.1:c.1264C>T
ENST00000336642.8:c.316C>T
ENST00000345378.6:c.1267C>T
ENST00000395796.7:c.1261C>T
ENST00000403799.7:c.1264C>T
ENST00000437084.1:c.1213C>T
ENST00000459642.1:n.644C>T
ENST00000616242.4:c.1261C>T
NM_000162.3:c.1264C>T
NM_033507.1:c.1267C>T
NM_033508.1:c.1261C>T
NM_000162.4:c.1264C>T
NM_001354800.1:c.1264C>T
NM_001354801.1:c.253C>T
NM_001354802.1:c.124C>T
NM_001354803.1:c.298C>T
NM_033507.2:c.1267C>T
NM_033508.2:c.1261C>T
NM_033507.3:c.1267C>T
NM_033508.3:c.1261C>T

NM_001354803.2:c.298C>T

Likely Pathogenic

Met criteria codes 5

PM5_Supporting PM2_Supporting PP2 PP3 PP4_Moderate

Not Met criteria codes 2

PM1 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 3.1*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1264C>T variant in the glucokinase, GCK, causes an amino acid change of arginine to tryptophan at codon 422 (p.Arg422Trp) 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 0.758, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 0.00000183, which is below the ClinGen MDEP threshold of 0.000003 (PM2_Supporting). This variant was identified in three unrelated individuals with hyperglycemia; however, this number is below the ClinGen MDEP threshold for PS4_Moderate (PMID: 36257325, internal lab contributors). At least one of these individuals had a phenotype highly consistent for GCK-related hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate, internal lab contributors). Another missense variant at the same residue, c.1265G>C (p.Arg422Pro), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.1264C>T 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, approved 10/10/2025): PP4_Moderate, PM2_Supporting, PM5_Supporting, PP2, PP3.

Met criteria codes

PM5_Supporting	✔	Another missense variant at the same residue, c.1265G>C (p.Arg422Pro), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
PM2_Supporting	✔	This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 0.00000183, which is below the ClinGen MDEP threshold of 0.000003 (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 0.758, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate	✔	This variant was identified in an individual with a phenotype highly consistent for GCK-related hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate, internal lab

contributors).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant was identified in three unrelated individuals with hyperglycemia; however, this number is below the ClinGen MDEP threshold for PS4_Moderate (PMID: 36257325, internal lab contributors).

Curation History

Showing 1 to 1 of 1 rows

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