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# *Variant: NM_000162.5(GCK):c.1265G>T (p.Arg422Leu)*

Version: 1.1

*CA157911892*

*1800884 (ClinVar)*

**Gene**: GCK (HGNC:2645)
**Condition**: monogenic diabetes (MONDO:0015967)
**Inheritance Mode**: Semidominant inheritance
**UUID:** e5079dda-99ad-4583-a42d-e93dbd143710
**Approved on**: Thu, 22 Oct 2026 00:00:00 +0000
**Published on**: Thu, 22 Oct 2026 00:00:00 +0000

## *HGVS expressions*

**NM_000162.5:c.1265G>T**
**NM_000162.5(GCK):c.1265G>T (p.Arg422Leu)**
NC_000007.14:g.44145269C>A
CM000669.2:g.44145269C>A
NC_000007.13:g.44184868C>A
CM000669.1:g.44184868C>A
NC_000007.12:g.44151393C>A
NG_008847.1:g.49155G>T
NG_008847.2:g.57902G>T
ENST00000395796.8:c.*1263G>T
ENST00000616242.5:c.*385G>T
ENST00000683378.1:n.491G>T
ENST00000336642.9:c.299G>T
ENST00000345378.7:c.1268G>T
ENST00000403799.8:c.1265G>T
ENST00000671824.1:c.1328G>T
ENST00000672743.1:n.277G>T
ENST00000673284.1:c.1265G>T
ENST00000336642.8:c.317G>T
ENST00000345378.6:c.1268G>T
ENST00000395796.7:c.1262G>T
ENST00000403799.7:c.1265G>T
ENST00000437084.1:c.1214G>T
ENST00000459642.1:n.645G>T
ENST00000616242.4:c.1262G>T
NM_000162.3:c.1265G>T
NM_033507.1:c.1268G>T
NM_033508.1:c.1262G>T
NM_000162.4:c.1265G>T
NM_001354800.1:c.1265G>T
NM_001354801.1:c.254G>T
NM_001354802.1:c.125G>T
NM_001354803.1:c.299G>T
NM_033507.2:c.1268G>T
NM_033508.2:c.1262G>T
NM_033507.3:c.1268G>T
NM_033508.3:c.1262G>T

NM_001354803.2:c.299G>T

**Likely Pathogenic**

**Met criteria codes** 5

PS4_Moderate PM5_Supporting PM2_Supporting PP2 PP4_Moderate

**Not Met criteria codes** 2

BP4 PP3

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.1265G>T variant in the glucokinase, GCK, causes an amino acid change of arginine to leucine at codon 422 (p.Arg422Leu) 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 has an incomputable gnomAD v4.1.2 Grpmax filtering allele frequency due to no more than one copy in any non-founder subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 23771925, 33218273, internal lab contributors). At least one of these individuals had a phenotype highly consistent for GCK-related hyperglycemia (persistent elevated fasting glucose 5.5-8 mmol/L (3x) and HbA1c 5.6 - 7.6% (4x)) (PP4_Moderate; PMID: 33218273). Another missense variant at the same residue, c.1265G>C (p.Arg422Pro), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). This variant has a REVEL score of 0.635, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function. In summary, c.1265G>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): PS4_Moderate, PP4_Moderate, PM2_Supporting, PM5_Supporting, PP2.**

**Met criteria codes**

| | |
|---|---|
| **PS4_Moderate** ✔ | This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 23771925, 33218273, internal lab contributors). |
| **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 an incomputable gnomAD v4.1.1 Grpmax filtering allele frequency due to no more than one copy in any non-founder subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 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). |
| **PP4_Moderate** ✔ | |

This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (persistent fasting glucose 5.5-8 mmol/L (3x) and HbA1c 5.6 - 7.6% (4x)) (PP4_Moderate; PMID: 33218273).

**Not Met criteria codes**

| | | |
|---|---|---|
| **BP4** | ✖ | This variant has a REVEL score of 0.635, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on HNF1A function. |
| **PP3** | ✖ | This variant has a REVEL score of 0.635, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on HNF1A function. |

Curation History

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