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Variant: NM_000162.5(GCK):c.1265G>C (p.Arg422Pro)

Version: 1.0

CA367397268

804841 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b99a6398-e148-4d21-983d-c9d913b82a57
Approved on: Tue, 29 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000162.5(GCK):c.1265G>C (p.Arg422Pro)
NM_000162.5:c.1265G>C
NC_000007.14:g.44145269C>G
CM000669.2:g.44145269C>G
NC_000007.13:g.44184868C>G
CM000669.1:g.44184868C>G
NC_000007.12:g.44151393C>G
NG_008847.1:g.49155G>C
NG_008847.2:g.57902G>C
ENST00000395796.8:c.*1263G>C
ENST00000616242.5:c.*385G>C
ENST00000683378.1:n.491G>C
ENST00000336642.9:c.299G>C
ENST00000345378.7:c.1268G>C
ENST00000403799.8:c.1265G>C
ENST00000671824.1:c.1328G>C
ENST00000672743.1:n.277G>C
ENST00000673284.1:c.1265G>C
ENST00000336642.8:c.317G>C
ENST00000345378.6:c.1268G>C
ENST00000395796.7:c.1262G>C
ENST00000403799.7:c.1265G>C
ENST00000437084.1:c.1214G>C
ENST00000459642.1:n.645G>C
ENST00000616242.4:c.1262G>C
NM_000162.3:c.1265G>C
NM_033507.1:c.1268G>C
NM_033508.1:c.1262G>C
NM_000162.4:c.1265G>C
NM_001354800.1:c.1265G>C
NM_001354801.1:c.254G>C
NM_001354802.1:c.125G>C
NM_001354803.1:c.299G>C
NM_033507.2:c.1268G>C
NM_033508.2:c.1262G>C
NM_033507.3:c.1268G>C
NM_033508.3:c.1262G>C

NM_001354803.2:c.299G>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP2 PP3 PS4_Moderate PP4_Moderate

Not Met criteria codes 1

PS3

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>C variant in the glucokinase, GCK, causes an amino acid change of arginine to proline at codon 422 (p.Arg422Pro) 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 0.786, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.1 (PM2_Supporting). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 26059258, DOI: 10.4274/BMJ.galenos.2023.2022.12-11, ClinVar, internal lab contributors). Additionally, at least one 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 autoantibodies (PP4_Moderate; internal lab contributors). A relative activity index (RAI) was calculated for this variant but the wild type parameters are not reported; therefore, this data cannot be used towards PS3 (PMID: 39371753). In summary, c.1265G>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 3.1, approved 10/10/2025): PS4_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (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 0.786, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4_Moderate	✔	This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 26059258, DOI: 10.4274/BMJ.galenos.2023.2022.12-11, ClinVar, 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 autoantibodies (PP4_Moderate; internal lab contributors).

Not Met criteria codes

PS3	ℹ	✖	A relative activity index (RAI) was calculated for this variant but the wild type parameters are not reported; therefore, this data cannot be used towards PS3 (PMID: 39371753).

Curation History

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