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# *Variant: NM_000162.5(GCK):c.1129C>A (p.Arg377Ser)*

Version: 2.0

*CA367398819*

*1727652 (ClinVar)*

**Gene**: GCK (HGNC:2645)
**Condition**: monogenic diabetes (MONDO:0015967)
**Inheritance Mode**: Semidominant inheritance
**UUID:** 3fd09c5a-7334-4761-a861-775841b44fdb
**Approved on**: Thu, 29 Oct 2026 00:00:00 +0000
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## *HGVS expressions*

**NM_000162.5(GCK):c.1129C>A (p.Arg377Ser)**
**NM_000162.5:c.1129C>A**
NC_000007.14:g.44145621G>T
CM000669.2:g.44145621G>T
NC_000007.13:g.44185220G>T
CM000669.1:g.44185220G>T
NC_000007.12:g.44151745G>T
NG_008847.1:g.48803C>A
NG_008847.2:g.57550C>A
ENST00000395796.8:c.*1127C>A
ENST00000616242.5:c.*249C>A
ENST00000683378.1:n.355C>A
ENST00000336642.9:c.163C>A
ENST00000345378.7:c.1132C>A
ENST00000403799.8:c.1129C>A
ENST00000671824.1:c.1192C>A
ENST00000672743.1:n.141C>A
ENST00000673284.1:c.1129C>A
ENST00000336642.8:c.181C>A
ENST00000345378.6:c.1132C>A
ENST00000395796.7:c.1126C>A
ENST00000403799.7:c.1129C>A
ENST00000437084.1:c.1078C>A
ENST00000459642.1:n.509C>A
ENST00000616242.4:c.1126C>A
NM_000162.3:c.1129C>A
NM_033507.1:c.1132C>A
NM_033508.1:c.1126C>A
NM_000162.4:c.1129C>A
NM_001354800.1:c.1129C>A
NM_001354801.1:c.118C>A
NM_001354802.1:c.-12C>A
NM_001354803.1:c.163C>A
NM_033507.2:c.1132C>A
NM_033508.2:c.1126C>A
NM_033507.3:c.1132C>A
NM_033508.3:c.1126C>A

NM_001354803.2:c.163C>A

**Pathogenic**

**Met criteria codes** 7

PP1_Strong PS4_Moderate PM5_Supporting PM2_Supporting PP2 PP3 PP4

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.1129C>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to proline at codon 377 (p.(Arg377Ser)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.988, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.2 (PM2_Supporting). This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 34746319, 35737141, internal lab contributors). Additionally, at least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; PMID: 34746319). This variant was segregated with hyperglycemia, with 6 informative meioses in two famlies (PP1_Strong; PMID: 34746319, internal lab contributors). Another missense variant at the same residue, c.1129C>T p.(Arg377Cys), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.Arg377Ser (PM5_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 3.1.0, approved 10/10/2025): PP2, PP3, PP4, PM2_Supporting, PS4_Moderate, PP1_Strong, PM5_Supporting.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1_Strong** | ✔ | This variant was segregated with hyperglycemia, with 6 informative meioses in two famlies (PP1_Strong; PMID: 34746319, internal lab contributors). |
| **PS4_Moderate** | ✔ | This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 34746319, 35737141, internal lab contributors) |
| **PM5_Supporting** | ✔ | Another missense variant, c.1129C>T p.Arg377Cys), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.Arg377Ser (PM5_Supporting). |
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v4.1.0 (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 0.988, which is greater than the MDEP VCEP threshold of 0.70 (PP3). |
| **PP4** | | ✔ | This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; PMID: 34746319). |

## Curation History

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