

Variant: *NM\_000162.5(GCK):c.790G>A (p.Gly264Ser)*

Version: 1.1

CA341589 [↗](#)

21078 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** a0bd4d0f-fd6d-43b1-b64a-12ff1f71245d

**Approved on:** 2023/11/2

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### *HGVS expressions*

**NM\_000162.5(GCK):c.790G>A (p.Gly264Ser)**

**NM\_000162.5:c.790G>A**

NC\_000007.14:g.44147723C>T

CM000669.2:g.44147723C>T

NC\_000007.13:g.44187322C>T

CM000669.1:g.44187322C>T

NC\_000007.12:g.44153847C>T

NG\_008847.1:g.46701G>A

NG\_008847.2:g.55448G>A

ENST00000395796.8:c.\*788G>A

ENST00000616242.5:c.790G>A

ENST00000345378.7:c.793G>A

ENST00000403799.8:c.790G>A

ENST00000671824.1:c.790G>A

ENST00000673284.1:c.790G>A

ENST00000345378.6:c.793G>A

ENST00000395796.7:c.787G>A

ENST00000403799.7:c.790G>A

ENST00000437084.1:c.739G>A

ENST00000616242.4:c.787G>A

NM\_000162.3:c.790G>A

NM\_033507.1:c.793G>A

NM\_033508.1:c.787G>A

NM\_000162.4:c.790G>A

NM\_001354800.1:c.790G>A

NM\_033507.2:c.793G>A

NM\_033508.2:c.787G>A

NM\_033507.3:c.793G>A

NM\_033508.3:c.787G>A

**Pathogenic**

Met criteria codes **7**

PM3\_Strong

PP1\_Strong

PP4\_Moderate

PP2

PP3

PS4

PM2\_Supporting

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Not Met criteria codes 2

PM1

PS3

Evidence Links 0

[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.790G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to serine at codon 264 (p.(Gly264Ser)) of NM\_000162.5. This variant is absent from gnomAD v2.1.1 (PM2\_Supporting). This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMID: 11508276, internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4\_Moderate, internal lab contributors). This variant segregated with diabetes/hyperglycemia, with 4 informative meioses in 2 families (PP1\_Strong; PMID: 16026363s, internal lab contributors). This variant has been detected in two individuals with neonatal diabetes. Both were compound heterozygous (confirmed in trans) for this variant and another variant classified as pathogenic by ClinGen MDEP (PM3\_Strong; PMIDs: 14578306, 16026363, internal lab contributors). 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 0.847, which is greater than the MDEP VCEP threshold of 0.70 (PP3). The Relative Activity Index (RAI) of this variant was found to be above the MDEP cutoff (0.5) for PS3\_Moderate. While the p.Gly264Ser variant has been reported to cause protein misfolding, this is not considered to meet criteria for applying PS3\_Supporting by the ClinGen MDEP (PMIDs: 22820548, 14578306, 16731834, <https://doi.org/10.1159/000079009>). In summary, c.790G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1\_Strong, PS4, PP4\_Moderate, PM3\_Strong, PP2, PP3, PM2\_Supporting.

**Met criteria codes**

**PM3\_Strong**



This variant has been detected in two individuals with neonatal diabetes. Both were compound heterozygous (confirmed in trans) for this variant and another variant classified as pathogenic by ClinGen MDEP (PM3\_Strong; PMIDs: 14578306, 16026363, internal lab contributors).

**PP1\_Strong**



This variant segregated with diabetes/hyperglycemia, with 4 informative meioses in 2 families (PP1\_Strong; PMID: 16026363s, internal lab contributors).

**PP4\_Moderate**



This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (internal lab contributors).

**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 0.847, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

**PS4**



This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMID: 11508276, internal lab contributors).

PM2\_Supporting

This variant is absent from gnomAD v2.1.1 (PM2\_Supporting).

Not Met criteria codes

PM1

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS3

The Relative Activity Index (RAI) of this variant was found to be above the MDEP cutoff (0.5) for PS3\_Moderate. While the p.Gly264Ser variant has been reported to cause protein misfolding, this is not considered to meet criteria for applying PS3\_Supporting by the ClinGen MDEP (PMIDs: 22820548, 14578306, 16731834, <https://doi.org/10.1159/000079009>).

Curation History

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| See Report           | Preferred Variant Title               | Classification | Condition          | Published Date | Version | Criteria Specification                                                                                                         | Gene |
|----------------------|---------------------------------------|----------------|--------------------|----------------|---------|--------------------------------------------------------------------------------------------------------------------------------|------|
| <a href="#">View</a> | NM_000162.5(GCK):c.790G>A (p.Gly26... | Pathogenic     | Monogenic Diabetes | 2023-11-02     | 1.1     | ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0 | GCK  |
| <a href="#">View</a> | NM_000162.5(GCK):c.790G>A (p.Gly26... | Pathogenic     | Monogenic Diabetes | 2023-10-13     | 1.0     | ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0 | GCK  |

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