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# *Variant: NM_000162.5(GCK):c.56T>A (p.Ile19Asn)*

Version: 1.0

*CA367403826*

*2136531 (ClinVar)*

**Gene**: GCK (HGNC:2645)
**Condition**: monogenic diabetes (MONDO:0015967)
**Inheritance Mode**: Semidominant inheritance
**UUID:** 588c71a8-9a58-4904-8a95-4da3714631e8
**Approved on**: 2026/2/24
**Published on**: 2026/2/26

## *HGVS expressions*

**NM_000162.5:c.56T>A**
**NM_000162.5(GCK):c.56T>A (p.Ile19Asn)**
NC_000007.14:g.44153453A>T
CM000669.2:g.44153453A>T
NC_000007.13:g.44193052A>T
CM000669.1:g.44193052A>T
NC_000007.12:g.44159577A>T
NG_008847.1:g.40971T>A
NG_008847.2:g.49718T>A
ENST00000395796.8:c.*54T>A
ENST00000616242.5:c.56T>A
ENST00000682635.1:n.542T>A
ENST00000345378.7:c.59T>A
ENST00000403799.8:c.56T>A
ENST00000671824.1:c.56T>A
ENST00000673284.1:c.56T>A
ENST00000345378.6:c.59T>A
ENST00000395796.7:c.53T>A
ENST00000403799.7:c.56T>A
ENST00000437084.1:c.56T>A
ENST00000476008.1:n.491T>A
ENST00000616242.4:c.53T>A
NM_000162.3:c.56T>A
NM_033507.1:c.59T>A
NM_033508.1:c.53T>A
NM_000162.4:c.56T>A
NM_001354800.1:c.56T>A
NM_033507.2:c.59T>A
NM_033508.2:c.53T>A
NM_033507.3:c.59T>A
NM_033508.3:c.53T>A

**Pathogenic**

**Met criteria codes** 7

PM3 PS4 PM2_Supporting PP1 PP2 PP3 PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

**Not Met criteria codes** 2

PM1 PS3

Evidence Links 0

Criteria Specification Information

- **Criteria Specification:** *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Monogenic Diabetes VCEP***

**The c.56T>A variant in the glucokinase gene, GCK, causes an amino acid change of isoleucine to asparagine at codon 19 (p.(Ile19Asn)) 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 v4.1.0 Grpmax filtering allele frequency due to no more than one copy in any subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.861, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMID: 25665835, 33852230, 17573900, internal lab contributors). 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 antibody) (PP4_Moderate; internal lab contributors), and segregated with hyperglycemia, with two informative meioses in two families (PP1; PMID: 25665835, internal lab contributors). This variant has been detected in two siblings with neonatal diabetes who were compound heterozygous (confirmed in trans) for this variant and c.1322C>G p.Ser441Trp, which was classified as pathogenic by the MDEP VCEP (PMID: 25665835) (PM3). The relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5 and a relative stability index was not calculated, so PS3 will not be applied (PMID: 25665835). In summary, c.56T>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4, PP4_moderate, PP1, PM3, PP2, PP3, PM2_Supporting.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM3** | ✔ | This variant has been detected in two siblings with neonatal diabetes who were compound heterozygous (confirmed in trans) for this variant and c.1322C>G p.Ser441Trp, which was classified as pathogenic by the MDEP VCEP (PMID: 25665835) (PM3). |
| **PS4** | ✔ | This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMID: 25665835, 33852230, 17573900, internal lab contributors). |
| **PM2_Supporting** | ✔ | This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no more than one copy in any subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). |
| **PP1** | ✔ | This variant segregated with hyperglycemia, with two informative meioses in two families (PP1; PMID: 25665835, 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 0.861, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

**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 antibody) (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

**PS3** ✖

The relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5 and a relative stability index was not calculated (PMID: 25665835).

Curation History

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