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# *Variant: NM_000162.5(GCK):c.562G>A (p.Ala188Thr)*

Version: 1.0

*CA4239604*

*804849 (ClinVar)*

**Gene**: GCK (HGNC:2645)
**Condition**: monogenic diabetes (MONDO:0015967)
**Inheritance Mode**: Semidominant inheritance
**UUID:** 24504115-2c42-4175-bedd-c3677f1a7b2e
**Approved on**: 2026/5/26
**Published on**: 2026/6/24

## *HGVS expressions*

**NM_000162.5(GCK):c.562G>A (p.Ala188Thr)**
**NM_000162.5:c.562G>A**
NC_000007.14:g.44149986C>T
CM000669.2:g.44149986C>T
NC_000007.13:g.44189585C>T
CM000669.1:g.44189585C>T
NC_000007.12:g.44156110C>T
NG_008847.1:g.44438G>A
NG_008847.2:g.53185G>A
ENST00000395796.8:c.*560G>A
ENST00000616242.5:c.562G>A
ENST00000682635.1:n.1048G>A
ENST00000345378.7:c.565G>A
ENST00000403799.8:c.562G>A
ENST00000671824.1:c.562G>A
ENST00000673284.1:c.562G>A
ENST00000345378.6:c.565G>A
ENST00000395796.7:c.559G>A
ENST00000403799.7:c.562G>A
ENST00000437084.1:c.511G>A
ENST00000616242.4:c.559G>A
NM_000162.3:c.562G>A
NM_033507.1:c.565G>A
NM_033508.1:c.559G>A
NM_000162.4:c.562G>A
NM_001354800.1:c.562G>A
NM_033507.2:c.565G>A
NM_033508.2:c.559G>A
NM_033507.3:c.565G>A
NM_033508.3:c.559G>A

**Pathogenic**

**Met criteria codes** 8

PP1_Strong | PS3_Moderate | PM3_Strong | PS4 | PM2_Supporting | PP2 | PP3 | PP4_Moderate

**Not Met criteria codes** 1

PM1

## Evidence Links 1

## 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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Monogenic Diabetes VCEP***

**The c.562G>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to threonine at codon 188 (p.(Ala188Thr)) 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 0.933, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Functional studies meeting MDEP wild type quality control measures showed that the relative activity Index (RAI) of this variant was 0, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 41516031). This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 2.81e-7, which is below the ClinGen MDEP threshold of 0.000003 (PM2_Supporting). This variant was identified in at least 66 individuals with hyperglycemia (PS4; PMID: 29207974, 39859454, 38752501, 36227502, 36836406, 34556497, 36257325, 35472491, 35592779, 34440516, 30257192, 28170077, 22761713, 20337973, 16602010, 14517956, 12955723, 12050210, 8933019, 8314448, ClinVar, internal lab contributors). Furthermore, at least two individuals 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 antibodies) (PP4_Moderate; internal lab contributors). This variant has been detected in at least 7 individuals with neonatal diabetes. Of those individuals, 6 were homozygous, and one was compound heterozygous for this variant and another variant classified as pathogenic (c.667G>A, p.Gly223Ser) by ClinGen MDEP (PM3_Strong; PMID: 38752501, Madani et al. 2018, internal lab contributors). Additionally, this variant segregated with hyperglycemia with at least 36 informative meioses in multiple families (PP1_Strong, PMID: 30257192, 36257325, Madani et al., 2018; internal lab contributors). In summary, c.562G>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, PM3_Strong, PP1_Strong, PS3_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1_Strong** | ✔ | This variant segregated with hyperglycemia with at least 36 informative meioses in multiple families (PP1_Strong, PMID: 30257192, 36257325, Madani et al., 2018; internal lab contributors). |
| **PS3_Moderate** | ✔ | MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 41516031).<br>MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0, which is below the MDEP cutoff (<0.5) PubMed:41516031 |
| **PM3_Strong** | ✔ | This variant has been detected in at least 7 individuals with neonatal diabetes. Of those individuals, 6 were homozygous, and one was compound heterozygous for this variant and another variant classified as pathogenic (c.667G>A, p.Gly223Ser) by ClinGen MDEP (PM3_Strong; PMID: 38752501, Madani et al. 2018, internal lab contributors). |

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|---|---|---|
| **PS4** | ✔ | This variant was identified in at least 66 individuals with hyperglycemia (PS4; PMID: 29207974, 39859454, 38752501, 36227502, 36836406, 34556497, 36257325, 35472491, 35592779, 34440516, 30257192, 28170077, 22761713, 20337973, 16602010, 14517956, 12955723, 12050210, 8933019, 8314448, ClinVar, internal lab contributors). |
| **PM2_Supporting** | ✔ | This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 2.81e-7, which is below the ClinGen MDEP threshold of 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). |
| **PP3** | ✔ | This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.933, which is greater than the MDEP VCEP threshold of 0.70 (PP3). |
| **PP4_Moderate** | ✔ | This variant was identified in at least two individuals with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM1** | ✖ | This variant does not reside in an amino acid that directly binds glucose or ATP, which are defined as critical for the GCK protein's function by the ClinGen MDEP. |

## Curation History

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| See Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | NM_000162.5(GCK):c.562G>A (p.Ala18... | Pathogenic | Monogenic Diabetes | 2026-06-24 | 1.0 | ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0 | GCK |

Showing 1 to 1 of 1 rows

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