Variant: NM_000162.5(GCK):c.864-1G>C

Version: 1.0

CA367400275

1700683 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: c3958899-d5c4-4e45-8cd5-3a8344defd55
Approved on: 2025-11-24
Published on: 2025-11-26

HGVS expressions

NM_000162.5:c.864-1G>C
NM_000162.5(GCK):c.864-1G>C
NC_000007.14:g.44146619C>G
CM000669.2:g.44146619C>G
NC_000007.13:g.44186218C>G
CM000669.1:g.44186218C>G
NC_000007.12:g.44152743C>G
NG_008847.1:g.47805G>C
NG_008847.2:g.56552G>C
ENST00000395796.8:c.*862-1G>C
ENST00000616242.5:c.854-1G>C
ENST00000683378.1:n.89G>C
ENST00000345378.7:c.867-1G>C
ENST00000403799.8:c.864-1G>C
ENST00000671824.1:c.927-1G>C
ENST00000673284.1:c.864-1G>C
ENST00000345378.6:c.867-1G>C
ENST00000395796.7:c.861-1G>C
ENST00000403799.7:c.864-1G>C
ENST00000437084.1:c.813-1G>C
ENST00000473353.1:n.162-1G>C
ENST00000616242.4:c.861-1G>C
NM_000162.3:c.864-1G>C
NM_033507.1:c.867-1G>C
NM_033508.1:c.861-1G>C
NM_000162.4:c.864-1G>C
NM_001354800.1:c.864-1G>C
NM_001354801.1:c.8G>C
NM_033507.2:c.867-1G>C
NM_033508.2:c.861-1G>C
NM_033507.3:c.867-1G>C
NM_033508.3:c.861-1G>C

Pathogenic

Met criteria codes 5

PM2_Supporting PS1_Supporting PP4 PVS1 PS4_Moderate

Not Met criteria codes 1

PP1

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

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.864-1G>C variant in the glucokinase gene, GCK, is predicted to remove a canonical splice acceptor site in NM_000162.5. This variant is predicted to cause an in-frame deletion of biologically-relevant exon 8 of 10, a region important for protein function (PVS1). This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no more than 1 copy in any subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 25850297, 36208030, 20337973, 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%) (PP4; internal lab contributors). This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors). The c.864-1G>A variant at the same canonical nucleotide has been classified as pathogenic for monogenic diabetes by the ClinGen MDEP, and c.864-1G>C has a similar predicted impact by Splice AI (PS1_Supporting). In summary, c.864-1G>C 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): PVS1, PS1_Supporting, PS4_Moderate, PM2_Supporting, PP4.

Met criteria codes

PM2_Supporting	ℹ	✓	This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no more than 1 copy in any subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting).
PS1_Supporting	ℹ	✓	The c.864-1G>A variant at the same canonical nucleotide has been classified as pathogenic for monogenic diabetes by the ClinGen MDEP, and c.864-1G>C has a similar predicted impact by Splice AI (PS1_Supporting).
PP4	ℹ	✓	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%) (PP4; internal lab contributors).
PVS1	ℹ	✓	This variant is predicted to cause an in-frame deletion of biologically-relevant exon 8 of 10, a region important for protein function (PVS1).
PS4_Moderate	ℹ	✓	This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 25850297, 36208030, 20337973, internal lab contributors).

Not Met criteria codes

PP1	ⓘ	✖	This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors).

Curation History

Showing 1 to 1 of 1 rows