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Variant: NM_000162.5(GCK):c.451T>C (p.Ser151Pro)

Version: 1.0

CA367401938

2136526 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: f8c0d4cf-55cb-4f31-83a8-a2327d7176dd
Approved on: 2026/7/27
Published on: 2026/7/30

HGVS expressions

NM_000162.5:c.451T>C
NM_000162.5(GCK):c.451T>C (p.Ser151Pro)
NC_000007.14:g.44150988A>G
CM000669.2:g.44150988A>G
NC_000007.13:g.44190587A>G
CM000669.1:g.44190587A>G
NC_000007.12:g.44157112A>G
NG_008847.1:g.43436T>C
NG_008847.2:g.52183T>C
ENST00000395796.8:c.*449T>C
ENST00000616242.5:c.451T>C
ENST00000682635.1:n.937T>C
ENST00000345378.7:c.454T>C
ENST00000403799.8:c.451T>C
ENST00000671824.1:c.451T>C
ENST00000673284.1:c.451T>C
ENST00000345378.6:c.454T>C
ENST00000395796.7:c.448T>C
ENST00000403799.7:c.451T>C
ENST00000437084.1:c.400T>C
ENST00000616242.4:c.448T>C
NM_000162.3:c.451T>C
NM_033507.1:c.454T>C
NM_033508.1:c.448T>C
NM_000162.4:c.451T>C
NM_001354800.1:c.451T>C
NM_033507.2:c.454T>C
NM_033508.2:c.448T>C
NM_033507.3:c.454T>C
NM_033508.3:c.448T>C

Likely Pathogenic

Met criteria codes 7

PP4_Moderate | PM2_Supporting | PS2_Supporting | PS4_Moderate | PM1 | PP2 | PP3

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.451T>C variant in the glucokinase gene, GCK, causes an amino acid change of serine to proline at codon 151 (p.(Ser151Pro)) 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 0.991, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no copies in the European non-Finnish subpopulation and one copy in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 19564454, 36257325, 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). This variant was identified as a de novo occurrence with unconfirmed parental relationships in an individual with hyperglycemia, but with insufficient clinical information to determine if the phenotype is highly specific for GCK-hyperglycemia (PS2_Supporting; internal lab contributors). In summary, c.451T>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4_moderate, PP4_Moderate, PM1, PS2_Supporting, PM2_supporting, PP2, PP3.

Met criteria codes

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).
PM2_Supporting ✔	This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no copies in the European non-Finnish subpopulation and one copy in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).
PS2_Supporting ✔	This variant was identified as a de novo occurrence with unconfirmed parental relationships in an individual with hyperglycemia, but with insufficient clinical information to determine if the phenotype is highly specific for GCK-hyperglycemia (PS2_Supporting; internal lab contributors).
PS4_Moderate ✔	This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 19564454, 36257325, internal lab contributors).
PM1 ✔	

This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).

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

Curation History

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