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Variant: NM_000162.5(GCK):c.457C>T (p.Pro153Ser)

Version: 2.0

CA213788

36221 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 911c47d8-2f5b-44e1-98f9-779085515110
Approved on: 2026/6/24
Published on: 2026/6/24

HGVS expressions

NM_000162.5(GCK):c.457C>T (p.Pro153Ser)
NM_000162.5:c.457C>T
NC_000007.14:g.44150982G>A
CM000669.2:g.44150982G>A
NC_000007.13:g.44190581G>A
CM000669.1:g.44190581G>A
NC_000007.12:g.44157106G>A
NG_008847.1:g.43442C>T
NG_008847.2:g.52189C>T
ENST00000395796.8:c.*455C>T
ENST00000616242.5:c.457C>T
ENST00000682635.1:n.943C>T
ENST00000345378.7:c.460C>T
ENST00000403799.8:c.457C>T
ENST00000671824.1:c.457C>T
ENST00000673284.1:c.457C>T
ENST00000345378.6:c.460C>T
ENST00000395796.7:c.454C>T
ENST00000403799.7:c.457C>T
ENST00000437084.1:c.406C>T
ENST00000616242.4:c.454C>T
NM_000162.3:c.457C>T
NM_033507.1:c.460C>T
NM_033508.1:c.454C>T
NM_000162.4:c.457C>T
NM_001354800.1:c.457C>T
NM_033507.2:c.460C>T
NM_033508.2:c.454C>T
NM_033507.3:c.460C>T
NM_033508.3:c.454C>T

Pathogenic

Met criteria codes 7

PP4_Moderate PM2_Supporting PS4 PM1 PP1 PP2 PP3

Not Met criteria codes 1

PM5

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.457C>T variant in the glucokinase gene, GCK, causes an amino acid change of proline to serine at codon 153 (p.(Pro153Ser)) 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 0.973, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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 is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in seven unrelated individuals with hyperglycemia (PS4; PMID: 28726111/28323911, 34440516; ClinVar; internal lab contributors). Furthermore, 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% and OGTT with minimal increment (<3 mmol/l) (PP4_Moderate; PMID: 34440516). This variant segregated with hyperglycemia with two informative meioses in two families (PP1; PMID: 34440516; internal lab contributors). Another missense variant at the same residue has classified as pathogenic (c.458C>A, p.(Pro153His); however, PM5 was not applied to avoid circularity as p.Pro153Ser variant contributed to the classification of the other variant. In summary, c.457C>T 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 8/11/2023): PS4, PP4_Moderate, PM1, PP1, PP2, PP3, PM2_Supporting.

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 OGTT with minimal increment (<3 mmol/l) (PP4_Moderate; PMID: 34440516).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4	✔	This variant was identified in seven unrelated individuals with hyperglycemia (PS4; PMIDs: 28726111/28323911, 34440516; ClinVar; 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).
PP1	✔	This variant segregated with hyperglycemia with two informative meioses in two families (PP1; PMID: 34440516; 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 0.973, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

PM5 ✖ Another missense variant at the same residue has classified as pathogenic (c.458C>A, p.(Pro153His); however, PM5 was not applied to avoid circularity as p.Pro153Ser variant contributed to the classification of the other variant.

Curation History

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