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# *Variant: NM_000162.5(GCK):c.455T>C (p.Phe152Ser)*

Version: 1.0

*CA367401925*

*1741488 (ClinVar)*

**Gene**: GCK (HGNC:2645)
**Condition**: monogenic diabetes (MONDO:0015967)
**Inheritance Mode**: Semidominant inheritance
**UUID:** b8a8c2fb-7517-4e9e-a2e5-a4a95d0a14cb
**Approved on**: 2024/4/18
**Published on**: 2024/4/18

## *HGVS expressions*

**NM_000162.5:c.455T>C**
**NM_000162.5(GCK):c.455T>C (p.Phe152Ser)**
NC_000007.14:g.44150984A>G
CM000669.2:g.44150984A>G
NC_000007.13:g.44190583A>G
CM000669.1:g.44190583A>G
NC_000007.12:g.44157108A>G
NG_008847.1:g.43440T>C
NG_008847.2:g.52187T>C
ENST00000395796.8:c.*453T>C
ENST00000616242.5:c.455T>C
ENST00000682635.1:n.941T>C
ENST00000345378.7:c.458T>C
ENST00000403799.8:c.455T>C
ENST00000671824.1:c.455T>C
ENST00000673284.1:c.455T>C
ENST00000345378.6:c.458T>C
ENST00000395796.7:c.452T>C
ENST00000403799.7:c.455T>C
ENST00000437084.1:c.404T>C
ENST00000616242.4:c.452T>C
NM_000162.3:c.455T>C
NM_033507.1:c.458T>C
NM_033508.1:c.452T>C
NM_000162.4:c.455T>C
NM_001354800.1:c.455T>C
NM_033507.2:c.458T>C
NM_033508.2:c.452T>C
NM_033507.3:c.458T>C
NM_033508.3:c.452T>C

**Pathogenic**

**Met criteria codes** 6

PP2 PP3 PM5 PP1_Strong PP4_Moderate PM2_Supporting

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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Monogenic Diabetes VCEP***

**The c.455T>C variant in the glucokinase gene, GCK, causes an amino acid change of phenylalanine to serine at codon 152 (p.(Phe152Ser)) 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 0.981, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibody) (PP4_Moderate; PMID: 21978167). This variant segregated with diabetes/hyperglycemia, with four informative meioses in two families (PP1_Strong; PMID: 21978167, internal lab contributors]). Another missense variant, c.454T>C p.(Phe152Leu) has been interpreted as pathogenic by the ClinGen MDEP, and p.(Phe152Ser) has an equal or greater Grantham distance (PM5). In summary, c.455T>C meets the criteria to be classified as a variant of pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM2_Supporting, PP3, PP2, PM5, PP4_Moderate, PP1_Strong.**

**Met criteria codes**

| | | |
|---|---|---|
| **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 0.981, which is greater than the MDEP VCEP threshold of 0.70 (PP3). |
| **PM5** | ✔ | Another missense variant, c.454T>C p.(Phe152Leu) has been interpreted as pathogenic by the ClinGen MDEP, and p.(Phe152Ser) has an equal or greater Grantham distance (PM5). |
| **PP1_Strong** | ✔ | This variant segregated with diabetes/hyperglycemia, with four informative meioses in two families with MODY (PP1_Strong; PMID: 21978167, internal lab contributors]). |
| **PP4_Moderate** | ✔ | This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibody) (PP4_Moderate; PMID: 21978167). |
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v2.1.1 (PM2_Supporting). |

## Curation History

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