

Variant: NM_000162.5(GCK):c.454T>C (p.Phe152Leu)

Version: 1.0

CA367401929 [↗](#)

995370 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

UUID: c45f79b0-c0a7-429f-8d11-0f0b09338025

Approved on: 2024/4/18

Published on: 2024/4/18

HGVS expressions

NM_000162.5(GCK):c.454T>C (p.Phe152Leu)

NM_000162.5:c.454T>C

NC_000007.14:g.44150985A>G

CM000669.2:g.44150985A>G

NC_000007.13:g.44190584A>G

CM000669.1:g.44190584A>G

NC_000007.12:g.44157109A>G

NG_008847.1:g.43439T>C

NG_008847.2:g.52186T>C

ENST00000395796.8:c.*452T>C

ENST00000616242.5:c.454T>C

ENST00000682635.1:n.940T>C

ENST00000345378.7:c.457T>C

ENST00000403799.8:c.454T>C

ENST00000671824.1:c.454T>C

ENST00000673284.1:c.454T>C

ENST00000345378.6:c.457T>C

ENST00000395796.7:c.451T>C

ENST00000403799.7:c.454T>C

ENST00000437084.1:c.403T>C

ENST00000616242.4:c.451T>C

NM_000162.3:c.454T>C

NM_033507.1:c.457T>C

NM_033508.1:c.451T>C

NM_000162.4:c.454T>C

NM_001354800.1:c.454T>C

NM_033507.2:c.457T>C

NM_033508.2:c.451T>C

NM_033507.3:c.457T>C

NM_033508.3:c.451T>C

Pathogenic

Met criteria codes 6

PM2_Supporting

PP1_Strong

PS4

PP4_Moderate

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 1.3.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.454T>C variant in the glucokinase gene, GCK, causes an amino acid change of phenylalanine to leucine at codon 152 (p.(Phe152Leu)) 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 0.992, 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 seven unrelated individuals with hyperglycemia (PS4; PMID: 16965331, internal lab contributors]). This variant segregated with diabetes/hyperglycemia, with at least four informative meioses in two families (PP1_Strong; internal lab contributors). 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; internal lab contributors]). In summary, c.454T>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): PP4_Moderate, PS4, PM2_Supporting, PP3, PP2, PP1_Strong.

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP1_Strong			This variant segregated with diabetes/hyperglycemia, with at least four informative meioses in two families (PP1_Strong; internal lab contributors).
PS4			This variant was identified in seven unrelated individuals with hyperglycemia (PS4; PMID: 16965331, 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; 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 0.992, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

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