

Variant: *NM_033508.3:c.451T>A*

Version: 1.0

CA367401928 [↗](#)

3233993 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 40c04e80-28b3-4dab-a174-fee3bfc754c0

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HGVS expressions

NM_033508.3:c.451T>A

NC_000007.14:g.44150985A>T

CM000669.2:g.44150985A>T

NC_000007.13:g.44190584A>T

CM000669.1:g.44190584A>T

NC_000007.12:g.44157109A>T

NG_008847.1:g.43439T>A

NG_008847.2:g.52186T>A

ENST00000395796.8:c.*452T>A

ENST00000616242.5:c.454T>A

ENST00000682635.1:n.940T>A

ENST00000345378.7:c.457T>A

ENST00000403799.8:c.454T>A

ENST00000671824.1:c.454T>A

ENST00000673284.1:c.454T>A

ENST00000345378.6:c.457T>A

ENST00000395796.7:c.451T>A

ENST00000403799.7:c.454T>A

ENST00000437084.1:c.403T>A

ENST00000616242.4:c.451T>A

NM_000162.3:c.454T>A

NM_033507.1:c.457T>A

NM_033508.1:c.451T>A

NM_000162.4:c.454T>A

NM_001354800.1:c.454T>A

NM_033507.2:c.457T>A

NM_033508.2:c.451T>A

NM_000162.5:c.454T>A

NM_033507.3:c.457T>A

Pathogenic

Met criteria codes **6**

PM2_Supporting

PP2

PP3

PP4

PM5_Strong

PM1

Evidence Links **0**

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.454T>A variant in the glucokinase gene, GCK, causes an amino acid change of phenylalanine to isoleucine at codon 153 (p.(Phe152Ile)) 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 0.994, 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 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 an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors). Two other missense variants, c.454T>C p.(Phe152Leu) and c.455T>C p.(Phe152Ser) have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong). In summary, c.454T>A meets the criteria to be classified as likely 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_Strong, PP4, PM1.

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
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 0.994, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4			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%) (PP4; internal lab contributors).
PM5_Strong			Two other missense variants, c.454T>C p.(Phe152Leu) and c.455T>C p.(Phe152Ser) have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong).
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).

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