

Variant: *NM_033508.3:c.772G>T*

Version: 1.0

CA367400582 [↗](#)

2578354 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: Oba69fad-66dd-47dd-990b-138e4e43da99

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HGVS expressions

NM_033508.3:c.772G>T

NC_000007.14:g.44147738C>A
CM000669.2:g.44147738C>A
NC_000007.13:g.44187337C>A
CM000669.1:g.44187337C>A
NC_000007.12:g.44153862C>A
NG_008847.1:g.46686G>T
NG_008847.2:g.55433G>T
ENST00000395796.8:c.*773G>T
ENST00000616242.5:c.775G>T
ENST00000345378.7:c.778G>T
ENST00000403799.8:c.775G>T
ENST00000671824.1:c.775G>T
ENST00000673284.1:c.775G>T
ENST00000345378.6:c.778G>T
ENST00000395796.7:c.772G>T
ENST00000403799.7:c.775G>T
ENST00000437084.1:c.724G>T
ENST00000616242.4:c.772G>T
NM_000162.3:c.775G>T
NM_033507.1:c.778G>T
NM_033508.1:c.772G>T
NM_000162.4:c.775G>T
NM_001354800.1:c.775G>T
NM_033507.2:c.778G>T
NM_033508.2:c.772G>T
NM_000162.5:c.775G>T
NM_033507.3:c.778G>T

Likely Pathogenic

Met criteria codes **4**

PP2 **PP3** **PP4** **PM5_Strong**

Not Met criteria codes **2**

PP1 **PM1**

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.775G>T variant in the glucokinase gene, GCK, causes an amino acid change of alanine to serine at codon 259 (p.(Ala259Ser)) of NM_000162.5. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.744, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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). Two other missense variants, c.776C>T p.Ala259Val and c.775G>A p.Ala259Thr, have been interpreted as pathogenic by the ClinGen MDEP, and p.Ala259Ser has a greater Grantham distance than p.Ala259Val and p.Ala259Thr (PM5_Strong). 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; PMID: 30245511). This variant segregated with hyperglycemia/diabetes with one informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 30245511). In summary, c.775G>T 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): PP3, PP2, PM5_Strong, PP4.

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 0.744, 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; PMID: 30245511).
PM5_Strong			Two other missense variants, c.776C>T p.Ala259Val and c.775G>A p.Ala259Thr, have been interpreted as pathogenic by the ClinGen MDEP, and p.Ala259Ser has a greater Grantham distance than p.Ala259Val and p.Ala259Thr (PM5_Strong).

Not Met criteria codes

PP1			This variant segregated with hyperglycemia/diabetes with one informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 30245511).
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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