

Variant: NM_001354803.2:c.352G>T

Version: 1.0

CA367397036 [↗](#)

2571652 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: dfd4e2d7-99fd-4e26-b10a-2621d16da6dc

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HGVS expressions

NM_001354803.2:c.352G>T

NC_000007.14:g.44145216C>A

CM000669.2:g.44145216C>A

NC_000007.13:g.44184815C>A

CM000669.1:g.44184815C>A

NC_000007.12:g.44151340C>A

NG_008847.1:g.49208G>T

NG_008847.2:g.57955G>T

ENST00000395796.8:c.*1316G>T

ENST00000616242.5:c.*438G>T

ENST00000683378.1:n.544G>T

ENST00000336642.9:c.352G>T

ENST00000345378.7:c.1321G>T

ENST00000403799.8:c.1318G>T

ENST00000671824.1:c.1381G>T

ENST00000672743.1:n.330G>T

ENST00000673284.1:c.1318G>T

ENST00000336642.8:c.370G>T

ENST00000345378.6:c.1321G>T

ENST00000395796.7:c.1315G>T

ENST00000403799.7:c.1318G>T

ENST00000437084.1:c.1267G>T

ENST00000459642.1:n.698G>T

ENST00000616242.4:c.1315G>T

NM_000162.3:c.1318G>T

NM_033507.1:c.1321G>T

NM_033508.1:c.1315G>T

NM_000162.4:c.1318G>T

NM_001354800.1:c.1318G>T

NM_001354801.1:c.307G>T

NM_001354802.1:c.178G>T

NM_001354803.1:c.352G>T

NM_033507.2:c.1321G>T

NM_033508.2:c.1315G>T

NM_000162.5:c.1318G>T

NM_033507.3:c.1321G>T

NM_033508.3:c.1315G>T

Pathogenic

Met criteria codes 5

PVS1

PP1_Strong

PP4_Moderate

PS4

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 1.2.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1318G>T variant in the glucokinase gene, GCK, results in a premature termination at codon 440 (p.(Glu440Ter)) of NM_000162.5. While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1). This variant is absent in gnomAD (PM2_Supporting). This variant was identified in at least two individuals with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). This variant was identified in 7 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 23890519, 25041077, DOI: 10.1530/endoabs.35.P371, and internal lab contributors). This variant segregated with diabetes, with 4 informative meioses in 4 families with MODY (PP1_Strong; PMID: 25041077, DOI: 10.1530/endoabs.35.P371, internal lab contributors). In summary, the c.1318G>T variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PVS1, PM2_Supporting, PP4_Moderate, PS4, PP1_Strong.

Met criteria codes

PVS1



While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1)

PP1_Strong



4 meioses in 4 families

PP4_Moderate



This variant was identified in at least two individuals with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors).

PS4



This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMIDs: 23890519, 25041077, DOI: 10.1530/endoabs.35.P371, internal lab contributors).

PM2_Supporting



absent in gnomAD

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