

Variant: *NM_033508.3:c.347G>T*

Version: 1.0

CA367402580 [↗](#)

2662928 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 76b79b12-022f-4884-a4d1-aee6107e003a

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HGVS expressions

NM_033508.3:c.347G>T

NC_000007.14:g.44152284C>A
CM000669.2:g.44152284C>A
NC_000007.13:g.44191883C>A
CM000669.1:g.44191883C>A
NC_000007.12:g.44158408C>A
NG_008847.1:g.42140G>T
NG_008847.2:g.50887G>T
ENST00000395796.8:c.*348G>T
ENST00000616242.5:c.350G>T
ENST00000682635.1:n.836G>T
ENST00000345378.7:c.353G>T
ENST00000403799.8:c.350G>T
ENST00000671824.1:c.350G>T
ENST00000673284.1:c.350G>T
ENST00000345378.6:c.353G>T
ENST00000395796.7:c.347G>T
ENST00000403799.7:c.350G>T
ENST00000437084.1:c.350G>T
ENST00000616242.4:c.347G>T
NM_000162.3:c.350G>T
NM_033507.1:c.353G>T
NM_033508.1:c.347G>T
NM_000162.4:c.350G>T
NM_001354800.1:c.350G>T
NM_033507.2:c.353G>T
NM_033508.2:c.347G>T
NM_000162.5:c.350G>T
NM_033507.3:c.353G>T

Likely Pathogenic

Met criteria codes **5**

PP2 PP3 PM2_Supporting
PS2_Moderate PP4_Moderate

Not Met criteria codes **2**

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

PS4

PM1

Evidence Links 0

[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.350G>T variant in the glucokinase gene, GCK, causes an amino acid change of glycine to valine at codon 117 (p.(Gly117Val)) 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 0.953, 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 two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 2 hour OGTT increment < 3 mmol/L and negative antibodies) (PP4_Moderate; internal lab contributors), identified as a de novo occurrence with unconfirmed parental relationships (PS2_Moderate, Internal lab contributors). In summary, c.350G>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, approved 8/11/2023): PP4_Moderate, PS2_Moderate, PP2, PP3, PM2_Supporting.

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 0.953, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS2_Moderate			This variant was identified as a de novo occurrence with unconfirmed parental relationships in an individual with a clinical picture highly specific for GCK-hyperglycemia ((FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 2 hour OGTT increment < 3 mmol/L and negative antibodies) (PS2_Moderate; 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 2 hour OGTT increment < 3 mmol/L and negative antibodies) (internal lab contributors).

Not Met criteria codes

PS4			This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).
PM1			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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