

Variant: NM_033508.3:c.107T>G

Version: 1.0

CA367403541 [↗](#)

2578357 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: cc7cd78c-8711-4e90-9c33-9b965a05da5d

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HGVS expressions

NM_033508.3:c.107T>G

NC_000007.14:g.44153399A>C
CM000669.2:g.44153399A>C
NC_000007.13:g.44192998A>C
CM000669.1:g.44192998A>C
NC_000007.12:g.44159523A>C
NG_008847.1:g.41025T>G
NG_008847.2:g.49772T>G
ENST00000395796.8:c.*108T>G
ENST00000616242.5:c.110T>G
ENST00000682635.1:n.596T>G
ENST00000345378.7:c.113T>G
ENST00000403799.8:c.110T>G
ENST00000671824.1:c.110T>G
ENST00000673284.1:c.110T>G
ENST00000345378.6:c.113T>G
ENST00000395796.7:c.107T>G
ENST00000403799.7:c.110T>G
ENST00000437084.1:c.110T>G
ENST00000476008.1:n.545T>G
ENST00000616242.4:c.107T>G
NM_000162.3:c.110T>G
NM_033507.1:c.113T>G
NM_033508.1:c.107T>G
NM_000162.4:c.110T>G
NM_001354800.1:c.110T>G
NM_033507.2:c.113T>G
NM_033508.2:c.107T>G
NM_000162.5:c.110T>G
NM_033507.3:c.113T>G

Pathogenic

Met criteria codes 6

PP1_Strong

PP4_Moderate

PS4_Moderate

PP2

PP3

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.110T>G variant in the glucokinase gene,GCK, causes an amino acid change of methionine to arginine at codon 37 (p.(Met37Arg)) of NM_000162.5. This variant segregated with diabetes, with at least four informative meioses in two families with MODY (PP1_Strong; internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and an OGTT with minimal increment) (PP4_Moderate; internal lab contributor). This variant was identified in four unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributor, DOI: 10.1055/s-2008-1004713). 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 0.9739, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). In summary, c.110T>G meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_Strong, PP4_Moderate, PS4_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes			
PP1_Strong			This variant segregated with diabetes, with at least four informative meioses in two families with MODY (PP1_Strong; internal lab contributors).
PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and an OGTT with minimal increment) (PP4_Moderate; internal lab contributor).
PS4_Moderate			This variant was identified in four unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributor, DOI: 10.1055/s-2008-1004713).
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 0.9739, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting			This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

Curation History 		
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