

Variant: NM_001354803.2:c.167C>A

Version: 1.0

CA367398804 [↗](#)

2664370 (ClinVar) [↗](#)

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

Condition: maturity-onset diabetes of the young type 2 ([MONDO:0007453](#))

Inheritance Mode: Semidominant inheritance

UUID: 7f5e3e97-4e94-4b0c-8cf9-53b52318d11f

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HGVS expressions

NM_001354803.2:c.167C>A

NC_000007.14:g.44145617G>T

CM000669.2:g.44145617G>T

NC_000007.13:g.44185216G>T

CM000669.1:g.44185216G>T

NC_000007.12:g.44151741G>T

NG_008847.1:g.48807C>A

NG_008847.2:g.57554C>A

ENST00000395796.8:c.*1131C>A

ENST00000616242.5:c.*253C>A

ENST00000683378.1:n.359C>A

ENST00000336642.9:c.167C>A

ENST00000345378.7:c.1136C>A

ENST00000403799.8:c.1133C>A

ENST00000671824.1:c.1196C>A

ENST00000672743.1:n.145C>A

ENST00000673284.1:c.1133C>A

ENST00000336642.8:c.185C>A

ENST00000345378.6:c.1136C>A

ENST00000395796.7:c.1130C>A

ENST00000403799.7:c.1133C>A

ENST00000437084.1:c.1082C>A

ENST00000459642.1:n.513C>A

ENST00000616242.4:c.1130C>A

NM_000162.3:c.1133C>A

NM_033507.1:c.1136C>A

NM_033508.1:c.1130C>A

NM_000162.4:c.1133C>A

NM_001354800.1:c.1133C>A

NM_001354801.1:c.122C>A

NM_001354802.1:c.-8C>A

NM_001354803.1:c.167C>A

NM_033507.2:c.1136C>A

NM_033508.2:c.1130C>A

NM_000162.5:c.1133C>A

NM_033507.3:c.1136C>A

NM_033508.3:c.1130C>A

Pathogenic

Met criteria codes 6

- PP4_Moderate
- PM5_Strong
- PP2
- PP3
- PS4_Moderate
- PM2_Supporting

Not Met criteria codes 1

- PP1

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.1133C>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to aspartic acid at codon 378 (p.(Ala378Asp)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.984, 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 5-6 unrelated individuals with hyperglycemia (PS4; internal lab contributors). The variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mol/L and HbA1c 5.6-7.6% and three-generation, dominant family history of diabetes or hyperglycemia (PP4_Moderate; internal lab contributors). This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (internal lab contributors). Two other missense variants, c.1133C>T (p.Ala378Val) and c.1132G>A (p.Ala378Thr) have been interpreted as pathogenic by the ClinGen MDEP, and p.Ala378Asp has an greater Grantham distance than p.Ala378Val and p.Ala378Thr (PM5_Strong). In summary, this variant meets the criteria to be classified as pathogenic for GCK-MODY. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PP2, PP3, PM2_Supporting, PP4_Moderate, PS4_moderate, PM5_Strong.

Met criteria codes

PP4_Moderate			The variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mol/L and HbA1c 5.6-7.6% and three-generation, dominant family history of diabetes or hyperglycemia. (PP4_Moderate; internal lab contributors).
PM5_Strong			Two other missense variants, c.1133C>T (p.Ala378Val) and c.1132G>A (p.Ala378Thr) have been interpreted as pathogenic by the ClinGen MDEP, and p.Ala378Asp has an greater Grantham distance than p.Ala378Val and p.Ala378Thr (PM5_Strong).
PP2			GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3			This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.984, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).

PS4_Moderate			This variant was identified in 6 unrelated individuals with hyperglycemia (PS4; internal lab contributors).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
Not Met criteria codes			
PP1			This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (internal lab contributors).

Curation History 
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