

Variant: NM_001354803.2:c.290T>C

Version: 1.1

CA367397309 [↗](#)

2571658 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: ac307cfc-2ced-4b4d-9325-a80acedffe42

Approved on: 2023/10/10

Published on: 2023/10/10

HGVS expressions

NM_001354803.2:c.290T>C

NC_000007.14:g.44145278A>G

CM000669.2:g.44145278A>G

NC_000007.13:g.44184877A>G

CM000669.1:g.44184877A>G

NC_000007.12:g.44151402A>G

NG_008847.1:g.49146T>C

NG_008847.2:g.57893T>C

ENST00000395796.8:c.*1254T>C

ENST00000616242.5:c.*376T>C

ENST00000683378.1:n.482T>C

ENST00000336642.9:c.290T>C

ENST00000345378.7:c.1259T>C

ENST00000403799.8:c.1256T>C

ENST00000671824.1:c.1319T>C

ENST00000672743.1:n.268T>C

ENST00000673284.1:c.1256T>C

ENST00000336642.8:c.308T>C

ENST00000345378.6:c.1259T>C

ENST00000395796.7:c.1253T>C

ENST00000403799.7:c.1256T>C

ENST00000437084.1:c.1205T>C

ENST00000459642.1:n.636T>C

ENST00000616242.4:c.1253T>C

NM_000162.3:c.1256T>C

NM_033507.1:c.1259T>C

NM_033508.1:c.1253T>C

NM_000162.4:c.1256T>C

NM_001354800.1:c.1256T>C

NM_001354801.1:c.245T>C

NM_001354802.1:c.116T>C

NM_001354803.1:c.290T>C

NM_033507.2:c.1259T>C

NM_033508.2:c.1253T>C

NM_000162.5:c.1256T>C

NM_033507.3:c.1259T>C

NM_033508.3:c.1253T>C

Likely Pathogenic

Met criteria codes 5

PP4_Moderate

PS3_Moderate

PP2

PP3

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 1.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c. 1256T>C variant in the glucokinase gene, GCK, causes an amino acid change of alanine to proline at codon 419 (p.(Phe419Ser)) 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 0.9739, 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 an individual 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; PMID: 22493702). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters passed the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Phe419Ser has RAI<0.01, which is less than the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID 22493702). This variant segregated with disease with two informative meioses in a single family with diabetes, however this does not meet the thresholds for PP1 set by the ClinGen MDEP VCEP (PMID: 27236918) (PMID 22493702). In summary, this variant meets the criteria to be classified as likely pathogenic for GCK-MODY. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2.0, approved 6/7/2023): PP2, PP3, PM2_Supporting, PP4_Moderate, PS3_Moderate.

Met criteria codes

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 negative antibodies) (PP4_Moderate; PMID: 22493702).
PS3_Moderate			A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Phe419Ser has RAI<0.01, which is less than or equal to the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID 22493702).
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 0.9739, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PP1			This variant segregated with disease with two informative meioses in a single family with diabetes, however this does not meet the thresholds for PP1 set by the ClinGen MDEP VCEP (PMID: 22493702).
-----	---	---	--

Curation History 

▼

▼

Showing 1 to 2 of 2 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.