

Variant: NM_000162.5(GCK):c.676G>A (p.Val226Met)

Version: 1.0

CA213827 [↗](#)

36243 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: a3bc2935-1bf2-4171-b759-ca1cfb249eb6

Approved on: 2023/8/13

Published on: 2023/8/13

HGVS expressions

NM_000162.5(GCK):c.676G>A (p.Val226Met)

NM_000162.5:c.676G>A

NC_000007.14:g.44149763C>T

CM000669.2:g.44149763C>T

NC_000007.13:g.44189362C>T

CM000669.1:g.44189362C>T

NC_000007.12:g.44155887C>T

NG_008847.1:g.44661G>A

NG_008847.2:g.53408G>A

ENST00000395796.8:c.*674G>A

ENST00000616242.5:c.676G>A

ENST00000682635.1:n.1162G>A

ENST00000345378.7:c.679G>A

ENST00000403799.8:c.676G>A

ENST00000671824.1:c.676G>A

ENST00000673284.1:c.676G>A

ENST00000345378.6:c.679G>A

ENST00000395796.7:c.673G>A

ENST00000403799.7:c.676G>A

ENST00000437084.1:c.625G>A

ENST00000616242.4:c.673G>A

NM_000162.3:c.676G>A

NM_033507.1:c.679G>A

NM_033508.1:c.673G>A

NM_000162.4:c.676G>A

NM_001354800.1:c.676G>A

NM_033507.2:c.679G>A

NM_033508.2:c.673G>A

NM_033507.3:c.679G>A

NM_033508.3:c.673G>A

Pathogenic

Met criteria codes 8

PP1_Strong

PS4

PP4_Moderate

PP2

PP3

PS3_Moderate

PM1

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 1.1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.676G>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to methionine at codon 261 (p.(Val226Met)) 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 0.789, which is greater than the MDEP threshold of 0.70 (PP3). This variant has a gnomAD v2.1.1 Popmax filtering allele frequency of 0.000002920 (below the MDEP threshold of 0.000003) and ≤ 2 copies observed in the European non-Finnish population and ≤ 1 copy in any other subpopulation, thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting). This variant was identified in more than 70 unrelated individuals with hyperglycemia (PS4; internal lab contributors). 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 negative antibodies) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes/hyperglycemia with more than 20 informative meioses in more than 30 families (PP1_Strong; internal lab contributors). This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein’s function by the ClinGen MDEP (PM1). 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.Val226Met variant has a relative activity index (RAI) of 0.009 to 0.198, which is less than the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID: 10525657, 25015100, https://doi.org/10.1159/isbn.978-3-318-01080-0). In summary, this variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PS4, PP1_Strong, PS3_Moderate, PM2_Supporting, PP2, PP4_Moderate, PP3, PM1.

Met criteria codes

PP1_Strong			This variant segregated with diabetes/hyperglycemia with more than 20 informative meioses in more than 30 families (PP1_Strong; internal lab contributors).
PS4			This variant was identified in more than 70 unrelated individuals with diabetes (PS4; 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 negative antibodies) (PP4_Moderate; internal lab contributors).
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 0.789, which is greater than the MDEP threshold of 0.70 (PP3).

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.Val226Met variant has a relative activity index (RAI) of 0.009 to 0.198, which is less than the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID: 10525657, 25015100, https://doi.org/10.1159/isbn.978-3-318-01080-0).
PM1			This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein’s function by the ClinGen MDEP (PM1).
PM2_Supporting			This variant has a gnomAD v2.1.1 Popmax filtering allele frequency of 0.000002920 (below the MDEP threshold of 0.000003) and ≤ 2 copies observed in the European non-Finnish population and ≤ 1 copy in any other subpopulation, thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting).

Curation History 	
<div><div></div><div><div></div><div> </div><div> </div></div></div>	
Showing 1 to 1 of 1 rows	
<div></div>	

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.