

Variant: NM_000162.5(GCK):c.626C>T (p.Thr209Met)

Version: 1.0

CA367401309 [↗](#)

804851 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 099a167c-4938-49f5-be6a-8ed18e2f2dd9

Approved on: 2025/6/27

Published on: 2025/6/27

HGVS expressions

NM_000162.5(GCK):c.626C>T (p.Thr209Met)

NM_000162.5:c.626C>T

NC_000007.14:g.44149813G>A

CM000669.2:g.44149813G>A

NC_000007.13:g.44189412G>A

CM000669.1:g.44189412G>A

NC_000007.12:g.44155937G>A

NG_008847.1:g.44611C>T

NG_008847.2:g.53358C>T

ENST00000395796.8:c.*624C>T

ENST00000616242.5:c.626C>T

ENST00000682635.1:n.1112C>T

ENST00000345378.7:c.629C>T

ENST00000403799.8:c.626C>T

ENST00000671824.1:c.626C>T

ENST00000673284.1:c.626C>T

ENST00000345378.6:c.629C>T

ENST00000395796.7:c.623C>T

ENST00000403799.7:c.626C>T

ENST00000437084.1:c.575C>T

ENST00000616242.4:c.623C>T

NM_000162.3:c.626C>T

NM_033507.1:c.629C>T

NM_033508.1:c.623C>T

NM_000162.4:c.626C>T

NM_001354800.1:c.626C>T

NM_033507.2:c.629C>T

NM_033508.2:c.623C>T

NM_033507.3:c.629C>T

NM_033508.3:c.623C>T

Pathogenic

Met criteria codes 7

PM6PP1_StrongPS4PM2_SupportingPP2PP3PP4_Moderate

Not Met criteria codes 1

PS2

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 2.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP		
<p>The c.626C>T variant in the glucokinase gene, GCK, causes an amino acid change of threonine to methionine at codon 209 (p.(Thr209Met)) of NM_000162.5. This variant was identified as a de novo occurrence with unconfirmed parental relationships in one individual with a clinical picture consistent with GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1C 5.6-7.6% and antibody negative) (PM6; internal lab contributors). This variant was identified in 25 unrelated individuals with hyperglycemia (PS4; PMIDs: 38550917, 8168652, 25174781, internal lab contributors). This variant is absent from gnomAD v2.1.1 and has an incomputable GrpMax filtering allele frequency in v4.1 due to one copy in the ENF subpopulation and no copies in any other subpopulation (PM2_Supporting). This variant segregated with hyperglycemia, with at least 12 informative meioses in 9 families (PP1_Strong; internal lab contributors). 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 0.985, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative) (PP4_Moderate; internal lab contributors). In summary, c.626C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 02/17/2025): PS4, PM6, PM2_Supporting, PM5_Supporting, PP1_Strong, PP2, PP3, PP4_Moderate.</p>		
Met criteria codes		
PM6	<div><div></div><div></div></div>	This variant was identified as a de novo occurrence with unconfirmed parental relationships in one individual with a clinical picture consistent with GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1C 5.6-7.6% and antibody negative) (PM6; internal lab contributors).
PP1_Strong	<div><div><div></div><div></div></div><div></div></div>	This variant segregated with hyperglycemia, with at least 12 informative meioses in 9 families (PP1_Strong; internal lab contributors).
PS4	<div><div><div></div><div></div></div><div></div></div>	This variant was identified in 25 unrelated individuals with hyperglycemia (PS4; PMID: 38550917, 8168652; 25174781; 38550917, internal lab contributors).
PM2_Supporting	<div><div><div></div><div></div></div><div></div></div>	This variant is absent from gnomAD v2.1.1 and has an incomputable GrpMax filtering allele frequency in v4.1 due to one copy in the ENF subpopulation and no copies in any other subpopulation (PM2_Supporting).
PP2	<div><div><div></div><div></div></div><div></div></div>	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 0.985, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative) (PP4_Moderate; internal lab contributors).
Not Met criteria codes			
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 			
			<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.