

Variant: *NM_000162.5(GCK):c.179C>T (p.Thr60Ile)*

Version: 1.0

CA4239709 [↗](#)

1343440 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

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HGVS expressions

NM_000162.5(GCK):c.179C>T (p.Thr60Ile)

NM_000162.5:c.179C>T

NC_000007.14:g.44153330G>A

CM000669.2:g.44153330G>A

NC_000007.13:g.44192929G>A

CM000669.1:g.44192929G>A

NC_000007.12:g.44159454G>A

NG_008847.1:g.41094C>T

NG_008847.2:g.49841C>T

ENST00000395796.8:c.*177C>T

ENST00000616242.5:c.179C>T

ENST00000682635.1:n.665C>T

ENST00000345378.7:c.182C>T

ENST00000403799.8:c.179C>T

ENST00000671824.1:c.179C>T

ENST00000673284.1:c.179C>T

ENST00000345378.6:c.182C>T

ENST00000395796.7:c.176C>T

ENST00000403799.7:c.179C>T

ENST00000437084.1:c.179C>T

ENST00000616242.4:c.176C>T

NM_000162.3:c.179C>T

NM_033507.1:c.182C>T

NM_033508.1:c.176C>T

NM_000162.4:c.179C>T

NM_001354800.1:c.179C>T

NM_033507.2:c.182C>T

NM_033508.2:c.176C>T

NM_033507.3:c.182C>T

NM_033508.3:c.176C>T

Pathogenic

Met criteria codes 7

PM2_SupportingPS3_SupportingPP1_StrongPS4PP2PP3PP4

Not Met criteria codes 1

PM1

Evidence Links 1

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.179C>T variant in the glucokinase gene, GCK causes an amino acid change of threonine to isoleucine at codon 60 (p.(Thr60Ile)) 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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to a single copy present in the South Asian population and 0 copies in any other subpopulation thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (gnomAD v4.1 Grpmax FAF ≤ 0.000003) (PM2_Supporting). This variant was identified in at least 11 unrelated individuals with hyperglycemia (PS4; PMID: 18248649, 34746319, internal lab contributors). At least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors). Additionally, this variant segregated with hyperglycemia with eight meioses in six families (PP1_Strong; PMID: 34746319, internal lab contributors). Functional studies of this variant demonstrate that it disrupts normal GK-GKRP binding (PS3_Supporting; PMID: 33273586). In summary, c.179C>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 2/17/2025): PS4, PP1_Strong, PP2, PP3, PP4 PM2_Supporting, PS3_Supporting.</p>		
Met criteria codes		
PM2_Supporting	<div><div></div><div></div></div>	This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to a single copy present in the South Asian population and 0 copies in any other subpopulation thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (gnomAD v4.1 Grpmax FAF ≤ 0.000003) (PM2_Supporting).
PS3_Supporting	<div><div></div><div></div></div>	Functional studies of this variant demonstrate that it disrupts normal GK-GKRP binding (PS3_Supporting; PMID: 33273586).
Disrupts GK-GKRP binding; T60I impairs both the enzymatic activity of glucokinase and its regulation by GKRP. PubMed:33273586		
PP1_Strong	<div><div></div><div></div></div>	This variant segregated with hyperglycemia with eight meioses in six families (PP1_Strong; PMID: 34746319, internal lab contributors).
PS4	<div><div></div><div></div></div>	This variant was identified in at least 11 unrelated individuals with hyperglycemia (PS4; PMID: 18248649, 34746319, internal lab contributors).
PP2	<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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

PP4



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%) (PP4; internal lab contributors).

Not Met criteria codes

PM1



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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