

Variant: *NM_000162.5(GCK):c.659G>A (p.Cys220Tyr)*

Version: 1.0

CA213822 [↗](#)

36240 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 24026d98-1810-45ed-99ad-5c8e8dfdd61b

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HGVS expressions

NM_000162.5:c.659G>A

NM_000162.5(GCK):c.659G>A (p.Cys220Tyr)

NC_000007.14:g.44149780C>T

CM000669.2:g.44149780C>T

NC_000007.13:g.44189379C>T

CM000669.1:g.44189379C>T

NC_000007.12:g.44155904C>T

NG_008847.1:g.44644G>A

NG_008847.2:g.53391G>A

ENST00000395796.8:c.*657G>A

ENST00000616242.5:c.659G>A

ENST00000682635.1:n.1145G>A

ENST00000345378.7:c.662G>A

ENST00000403799.8:c.659G>A

ENST00000671824.1:c.659G>A

ENST00000673284.1:c.659G>A

ENST00000345378.6:c.662G>A

ENST00000395796.7:c.656G>A

ENST00000403799.7:c.659G>A

ENST00000437084.1:c.608G>A

ENST00000616242.4:c.656G>A

NM_000162.3:c.659G>A

NM_033507.1:c.662G>A

NM_033508.1:c.656G>A

NM_000162.4:c.659G>A

NM_001354800.1:c.659G>A

NM_033507.2:c.662G>A

NM_033508.2:c.656G>A

NM_033507.3:c.662G>A

NM_033508.3:c.656G>A

Pathogenic

Met criteria codes 6

PS4PP2PP3PP4_ModeratePM2_SupportingPM5_Supporting

Not Met criteria codes 2

PS3PM1

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 3.1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.659G>A variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to tyrosine at codon 220 (p.(Cys220Tyr)) 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 0.841, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1 (PM2_Supporting). This variant was identified in seven unrelated individuals with hyperglycemia (PS4; PMID: 22341299, 31957151, 36836406, 36342518, 37008541, ClinVar, 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 OGTT with minimal increment (<3 mmol/L) (PP4_Moderate; PMID: 22341299). Another missense variant, c.658T>C p.Cys220Arg, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.659G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4, PP2, PP3, PP4_Moderate, PM2_Supporting, PM5_Supporting.

Met criteria codes

PS4

This variant was identified in seven unrelated individuals with hyperglycemia (PS4; PMID: 22341299, 31957151, 36836406, 36342518, 37008541, ClinVar, 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 0.841, 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 (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT with minimal increment (<3 mmol/L) (PP4_Moderate; PMID: 22341299).

PM2_Supporting

This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

PM5_Supporting

Another missense variant, c.658T>C p.Cys220Arg, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).

Not Met criteria codes

PS3



A relative activity index (RAI) was calculated for this variant but the wild type parameters are outside of MDEP's recommendations; therefore, this data cannot be used towards PS3 (PMID: 36342518).

Kcat for WT<40, therefore, PS3/BS3 cannot be applied [PubMed:36342518](#)

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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Showing 1 to 1 of 1 rows

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