

Variant: NM_000162.5(GCK):c.1015G>A (p.Glu339Lys)

Version: 1.0

CA130526 [↗](#)

39759 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: de2ef5ae-0b5f-480e-a9be-d46ce2d9f3e0

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HGVS expressions

NM_000162.5:c.1015G>A

NM_000162.5(GCK):c.1015G>A (p.Glu339Lys)

NC_000007.14:g.44146467C>T

CM000669.2:g.44146467C>T

NC_000007.13:g.44186066C>T

CM000669.1:g.44186066C>T

NC_000007.12:g.44152591C>T

NG_008847.1:g.47957G>A

NG_008847.2:g.56704G>A

ENST00000395796.8:c.*1013G>A

ENST00000616242.5:c.*135G>A

ENST00000683378.1:n.241G>A

ENST00000345378.7:c.1018G>A

ENST00000403799.8:c.1015G>A

ENST00000671824.1:c.1078G>A

ENST00000673284.1:c.1015G>A

ENST00000345378.6:c.1018G>A

ENST00000395796.7:c.1012G>A

ENST00000403799.7:c.1015G>A

ENST00000437084.1:c.964G>A

ENST00000473353.1:n.313G>A

ENST00000616242.4:c.1012G>A

NM_000162.3:c.1015G>A

NM_033507.1:c.1018G>A

NM_033508.1:c.1012G>A

NM_000162.4:c.1015G>A

NM_001354800.1:c.1015G>A

NM_001354801.1:c.8+152G>A

NM_033507.2:c.1018G>A

NM_033508.2:c.1012G>A

NM_033507.3:c.1018G>A

NM_033508.3:c.1012G>A

Likely Pathogenic

Met criteria codes 5

PP4_Moderate

PP2

PP3

PP1_Moderate

PM2_Supporting

Not Met criteria codes 3

PS3

PS4

PM1

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 1.2.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1015G>A variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of glutamic acid to lysine at codon 339 (p. (Glu339Lys)) of NM_000545.8. 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 0.963, which is greater than the MDEP VCEP threshold of 0.70 (PP3). While studies exploring the effect of this variant on protein function have been performed, these studies do not meet the criteria set forth by the MDEP for the application of PS3 or BS3 (PMID: 221104275). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (MDEP, PMIDs: 21104275, 34362814). This variant segregated with hyperglycemia, with 4 informative meioses in one family (PP1_Moderate; PMID: 21104275). The 5 individuals with the variant in this family had a clinical history highly specific for GCK-hyperglycemia (all FBG 5.5-8 mmol/L and mean HbA1c 5.6 - 7.6% and antibody-negative)(PP4_Moderate, PMID: 21104275). In summary, c.1015G>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_Moderate, PP4_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PP4_Moderate

This variant was identified in a family of five related individuals with a clinical history highly specific for GCK-hyperglycemia (all FBG 5.5-8 mmol/L and mean HbA1c 5.6 - 7.6% and antibody-negative) (PP4_Moderate; PMID: 21104275).

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 0.963, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

PP1_Moderate

This variant segregated with hyperglycemia, with 4 informative meioses in one family with MODY (PP1_Moderate; PMID: 21104275).

PM2_Supporting

This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS3			While studies exploring the effect of this variant on protein function have been performed, these studies do not meet the criteria set forth by the MDEP for the application of PS3 or BS3 (PMID: 221104275).
PS4			This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs: 21104275, 34362814).
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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