The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000162.5(GCK):c.688T>C (p.Cys230Arg)

Version: 1.0

CA247034

198397 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 2006eb6e-a43f-406e-af72-16f6c0e1e853
Approved on: 2023/12/2
Published on: 2023/12/2

HGVS expressions

NM_000162.5(GCK):c.688T>C (p.Cys230Arg)
NM_000162.5:c.688T>C
NC_000007.14:g.44147825A>G
CM000669.2:g.44147825A>G
NC_000007.13:g.44187424A>G
CM000669.1:g.44187424A>G
NC_000007.12:g.44153949A>G
NG_008847.1:g.46599T>C
NG_008847.2:g.55346T>C
ENST00000395796.8:c.*686T>C
ENST00000616242.5:c.688T>C
ENST00000345378.7:c.691T>C
ENST00000403799.8:c.688T>C
ENST00000671824.1:c.688T>C
ENST00000673284.1:c.688T>C
ENST00000345378.6:c.691T>C
ENST00000395796.7:c.685T>C
ENST00000403799.7:c.688T>C
ENST00000437084.1:c.637T>C
ENST00000616242.4:c.685T>C
NM_000162.3:c.688T>C
NM_033507.1:c.691T>C
NM_033508.1:c.685T>C
NM_000162.4:c.688T>C
NM_001354800.1:c.688T>C
NM_033507.2:c.691T>C
NM_033508.2:c.685T>C
NM_033507.3:c.691T>C
NM_033508.3:c.685T>C

Likely Pathogenic

Met criteria codes 5

PM1 PM5_Supporting PM2_Supporting PP2 PP3

Not Met criteria codes 2

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS4 PP4

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.688T>C variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to arginine at codon 230 (p.(Cys230Arg)) 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 resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1), and is predicted to be deleterious by computational evidence, with a REVEL score of 0.85, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in three unrelated individuals with hyperglycemia; however, this does not meet the threshold set by the ClinGen MDEP for the application of PS4 (internal lab contributors). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, the fasting blood sugar was slightly below the threshold for PP4 (5.5 mmol/L) (internal lab contributors). Another missense variant, c.689G>A p.Cys230Tyr, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Cys230Arg (PM5_Supporting). In summary, c.688T>C 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): PM1, PP2, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

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).
PM5_Supporting	✔	c.689G>A p.Cys230Tyr is pathogenic GD = 194 c.688T>C p.Cys230Arg GD = 180 Another missense variant, c.689G>A p.Cys230Tyr, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Cys230Arg (PM5_Supporting).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
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 0.85, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

PS4	✖	2 cases at Invitae, 1 case at GeneDx. 3 cases at Athena but affected status is unknown. This variant was identified in three unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (Internal lab contributors).
PP4	✖	This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, the fasting blood sugar was slightly below the threshold for PP4 (5.5 mmol/L) (internal lab contributors).

Curation History

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