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.389T>C (p.Ile130Thr)

Version: 1.0

CA157918200

1704126 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e9744df7-5d66-4ddf-8ddf-eca9fab38ecc
Approved on: 2024/2/28
Published on: 2024/2/28

HGVS expressions

NM_000162.5(GCK):c.389T>C (p.Ile130Thr)
NM_000162.5:c.389T>C
NC_000007.14:g.44151050A>G
CM000669.2:g.44151050A>G
NC_000007.13:g.44190649A>G
CM000669.1:g.44190649A>G
NC_000007.12:g.44157174A>G
NG_008847.1:g.43374T>C
NG_008847.2:g.52121T>C
ENST00000395796.8:c.*387T>C
ENST00000616242.5:c.389T>C
ENST00000682635.1:n.875T>C
ENST00000345378.7:c.392T>C
ENST00000403799.8:c.389T>C
ENST00000671824.1:c.389T>C
ENST00000673284.1:c.389T>C
ENST00000345378.6:c.392T>C
ENST00000395796.7:c.386T>C
ENST00000403799.7:c.389T>C
ENST00000437084.1:c.364-26T>C
ENST00000616242.4:c.386T>C
NM_000162.3:c.389T>C
NM_033507.1:c.392T>C
NM_033508.1:c.386T>C
NM_000162.4:c.389T>C
NM_001354800.1:c.389T>C
NM_033507.2:c.392T>C
NM_033508.2:c.386T>C
NM_033507.3:c.392T>C
NM_033508.3:c.386T>C

Likely Pathogenic

Met criteria codes 6

PP2 PP3 PS3_Moderate PP4_Moderate PM2_Supporting PS4_Moderate

Not Met criteria codes 2

PP1 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.389T>CT variant in the glucokinase gene, GCK, causes an amino acid change of isoleucine to threonine at codon 130 (p.(Ile130Thr)) 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 0.932, which is greater than the MDEP VCEP threshold of 0.70 (PP3). MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.17, which is below the MDEP cutoff (<0.5) (PMID: 22291974). This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in at least 6 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 36257325, 19790256, 14517956, 22291974, 34362814, internal lab contributor). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L) (PP4_Moderate; PMID: 22291974). In summary, c.389T>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, approved 8/11/2023): PP4_Moderate, PS3_Moderate, PS4_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

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 0.932, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.17, which is below the MDEP cutoff (<0.5) (PMID: 22291974).
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 increment < 3 mmol/L) (PP4_Moderate; PMID: 22291974).
PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).

PS4_Moderate		✔	This variant was identified in at least 6 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 36257325, 19790256, 14517956, 22291974, 34362814, internal lab contributor).

Not Met criteria codes

PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.