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_001354803.2:c.145T>C

Version: 1.0

CA367398947

2578362 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0430392f-97ae-4337-9960-d87aeb030b65
Approved on: 2023/8/9
Published on: 2023/8/10

HGVS expressions

NM_001354803.2:c.145T>C
NC_000007.14:g.44145639A>G
CM000669.2:g.44145639A>G
NC_000007.13:g.44185238A>G
CM000669.1:g.44185238A>G
NC_000007.12:g.44151763A>G
NG_008847.1:g.48785T>C
NG_008847.2:g.57532T>C
ENST00000395796.8:c.*1109T>C
ENST00000616242.5:c.*231T>C
ENST00000683378.1:n.337T>C
ENST00000336642.9:c.145T>C
ENST00000345378.7:c.1114T>C
ENST00000403799.8:c.1111T>C
ENST00000671824.1:c.1174T>C
ENST00000672743.1:n.123T>C
ENST00000673284.1:c.1111T>C
ENST00000336642.8:c.163T>C
ENST00000345378.6:c.1114T>C
ENST00000395796.7:c.1108T>C
ENST00000403799.7:c.1111T>C
ENST00000437084.1:c.1060T>C
ENST00000459642.1:n.491T>C
ENST00000616242.4:c.1108T>C
NM_000162.3:c.1111T>C
NM_033507.1:c.1114T>C
NM_033508.1:c.1108T>C
NM_000162.4:c.1111T>C
NM_001354800.1:c.1111T>C
NM_001354801.1:c.100T>C
NM_001354802.1:c.-30T>C
NM_001354803.1:c.145T>C
NM_033507.2:c.1114T>C
NM_033508.2:c.1108T>C
NM_000162.5:c.1111T>C
NM_033507.3:c.1114T>C
NM_033508.3:c.1108T>C

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

PP1

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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1111T>C variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to arginine at codon 371 (p.(Cys371Arg)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.98, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 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 negative antibodies) (internal lab contributors). Another missense variant, c.1112G>T p.(Cys371Phe), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.(Cys371Arg) (PM5_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2.0, approved 6/7/2023): PP2, PP3, PM2_Supporting, PP4_Moderate, PM5_Supporting.

Met criteria codes

PP2	✔	GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.98, 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 negative antibodies) (internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.1112G>T p.(Cys371Phe), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.(Cys371Arg)(PM5_Supporting).

Not Met criteria codes

PP1		✖	This variant segregated with diabetes/hyperglycemia with one informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors).

Curation History

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