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.503C>T (p.Thr168Ile)

Version: 1.0

CA367401750

1490297 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 013ccb72-f009-4e24-af55-2fef3fc8abde
Approved on: 2023/12/1
Published on: 2023/12/1

HGVS expressions

NM_000162.5(GCK):c.503C>T (p.Thr168Ile)
NM_000162.5:c.503C>T
NC_000007.14:g.44150045G>A
CM000669.2:g.44150045G>A
NC_000007.13:g.44189644G>A
CM000669.1:g.44189644G>A
NC_000007.12:g.44156169G>A
NG_008847.1:g.44379C>T
NG_008847.2:g.53126C>T
ENST00000395796.8:c.*501C>T
ENST00000616242.5:c.503C>T
ENST00000682635.1:n.989C>T
ENST00000345378.7:c.506C>T
ENST00000403799.8:c.503C>T
ENST00000671824.1:c.503C>T
ENST00000673284.1:c.503C>T
ENST00000345378.6:c.506C>T
ENST00000395796.7:c.500C>T
ENST00000403799.7:c.503C>T
ENST00000437084.1:c.452C>T
ENST00000616242.4:c.500C>T
NM_000162.3:c.503C>T
NM_033507.1:c.506C>T
NM_033508.1:c.500C>T
NM_000162.4:c.503C>T
NM_001354800.1:c.503C>T
NM_033507.2:c.506C>T
NM_033508.2:c.500C>T
NM_033507.3:c.506C>T
NM_033508.3:c.500C>T

Pathogenic

Met criteria codes 7

PM2_Supporting | PP2 | PP3 | PP4 | PM5_Strong | PM1 | PS4_Moderate

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.503C>T variant in the glucokinase gene, GCK, causes an amino acid change of threonine to isoleucine at codon 168 (p.(Thr168Ile)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 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 0.997 which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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). 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%) (PP4; internal lab contributors). This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors). Two other missense variants, c.502A>G p.Thr168Ala and c.503C>A p.Thr168Asn, have been interpreted as pathogenic by the ClinGen MDEP, and p.Thr168Ile has a greater Grantham distance than p.Thr168Ala and p.Thr168Asn (PM5_Strong). In summary, c.503C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM2_Supporting, PP2, PP3, PM1, PP4, PS4_Moderate, PM5_Strong.

Met criteria codes

PM2_Supporting ✔	This variant is absent from 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 0.997 which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4 ✔	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%) (PP4; internal lab contributors).
PM5_Strong ✔	Two other missense variants, c.502A>G p.Thr168Ala and c.503C>A p.Thr168Asn, have been interpreted as pathogenic by the ClinGen MDEP, and p.Thr168Ile has a greater Grantham distance than p.Thr168Ala and p.Thr168Asn (PM5_Strong).
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).

PS4_Moderate		✔	This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors).

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.