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_033508.3:c.500C>A

Version: 1.0

CA367401747

2682649 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 3167542c-9524-4f73-887b-0fec213ecaa1
Approved on: 2023/12/8
Published on: 2023/12/8

HGVS expressions

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

Pathogenic

Met criteria codes 7

PM1 PM5 PP1_Strong PM2_Supporting PP2 PP3 PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Evidence Links 0

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>A variant in the glucokinase gene, GCK, causes an amino acid change of threonine to asparagine at codon 168 (p.(Thr168Asn)) of NM_000162.5. 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 is predicted to be deleterious by computational evidence, with a REVEL score of 0.879, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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). Another missense variant, c.502A>G p.Thr168Ala, has been interpreted as pathogenic by the ClinGen MDEP, and p.Thr168Asn has a greater Grantham distance (PM5). 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) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes/hyperglycemia, with 6 informative meioses in one family with MODY (PP1_Strong; internal lab contributors). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, c.503C>A 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): PM1, PP3, PP2, PM5, PP4_Moderate, PP1_Strong, PM2_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	✔	Another missense variant, c.502A>G p.Thr168Ala, has been interpreted as pathogenic by the ClinGen MDEP, and p.Thr168Asn has a greater Grantham distance (PM5).
PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia, with 6 informative meioses in one family with MODY (PP1_Strong; internal lab contributors).
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 0.879, 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) (PP4_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.