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.362T>C

Version: 1.0

CA367402227

2735019 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5a488846-c719-4d87-9e91-0d8bba69660f
Approved on: 2024/3/7
Published on: 2024/3/7

HGVS expressions

NM_033508.3:c.362T>C
NC_000007.14:g.44151074A>G
CM000669.2:g.44151074A>G
NC_000007.13:g.44190673A>G
CM000669.1:g.44190673A>G
NC_000007.12:g.44157198A>G
NG_008847.1:g.43350T>C
NG_008847.2:g.52097T>C
ENST00000395796.8:c.*363T>C
ENST00000616242.5:c.365T>C
ENST00000682635.1:n.851T>C
ENST00000345378.7:c.368T>C
ENST00000403799.8:c.365T>C
ENST00000671824.1:c.365T>C
ENST00000673284.1:c.365T>C
ENST00000345378.6:c.368T>C
ENST00000395796.7:c.362T>C
ENST00000403799.7:c.365T>C
ENST00000437084.1:c.364-50T>C
ENST00000616242.4:c.362T>C
NM_000162.3:c.365T>C
NM_033507.1:c.368T>C
NM_033508.1:c.362T>C
NM_000162.4:c.365T>C
NM_001354800.1:c.365T>C
NM_033507.2:c.368T>C
NM_033508.2:c.362T>C
NM_000162.5:c.365T>C
NM_033507.3:c.368T>C

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PM2 PP4_Moderate PM5_Supporting

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 1.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.365T>C variant in the glucokinase gene, GCK, causes an amino acid change of leucine to proline at codon 122 (p.(Leu122Pro)) 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 0.98, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in 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 three-generation, dominant family history of diabetes or hyperglycemia) (PP4_Moderate; internal lab contributors). Another missense variant, c.364C>T, p.Leu122Phe has been interpreted as likely pathogenic by the ClinGen MDEP (PM5_Supporting). Taken together, this evidence supports the classification of c.365T>C 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): PM5_Supporting, PP4_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 0.98, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). absent from gnomAD v4.0.0
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 three-generation, dominant family history of diabetes or hyperglycemia) (PP4_Moderate; internal lab contributors).
PM5_Supporting	✔	Another missense variant, c.364C>T, p.Leu122Phe has been interpreted as likely pathogenic by the ClinGen MDEP (PM5_Supporting).

Curation History

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