

Variant: *NM_033508.3:c.361C>T*

Version: 1.0

CA367402230 [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

UUID: 2ded9569-8038-4c80-ba47-1aa96956465a

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HGVS expressions

NM_033508.3:c.361C>T

NC_000007.14:g.44151075G>A
CM000669.2:g.44151075G>A
NC_000007.13:g.44190674G>A
CM000669.1:g.44190674G>A
NC_000007.12:g.44157199G>A
NG_008847.1:g.43349C>T
NG_008847.2:g.52096C>T
ENST00000395796.8:c.*362C>T
ENST00000616242.5:c.364C>T
ENST00000682635.1:n.850C>T
ENST00000345378.7:c.367C>T
ENST00000403799.8:c.364C>T
ENST00000671824.1:c.364C>T
ENST00000673284.1:c.364C>T
ENST00000345378.6:c.367C>T
ENST00000395796.7:c.361C>T
ENST00000403799.7:c.364C>T
ENST00000437084.1:c.364-51C>T
ENST00000616242.4:c.361C>T
NM_000162.3:c.364C>T
NM_033507.1:c.367C>T
NM_033508.1:c.361C>T
NM_000162.4:c.364C>T
NM_001354800.1:c.364C>T
NM_033507.2:c.367C>T
NM_033508.2:c.361C>T
NM_000162.5:c.364C>T
NM_033507.3:c.367C>T

Likely Pathogenic

Met criteria codes 5

PP1_Strong

PP2

PP3

PS4_Moderate

PM2_Supporting

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

PP4

Evidence Links 0

- [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.364C>T variant in the glucokinase gene, GCK, causes an amino acid change of leucine to phenylalanine at codon 122 (p.(Leu122Phe)) 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 0.954, 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 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 29927023, 31905448, internal lab contributors). However, PP4 is unable to be evaluated due to insufficient clinical information. This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in 3 families (PP1_Strong; PMID: 31905448, internal lab contributors). In summary, c.364C>T meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0 approved 8/11/2023): PP1_Strong, PS4_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PP1_Strong			This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in 3 families (PP1_Strong; PMID: 31905448, internal lab contributors).
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 0.954, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4_Moderate			This variant was identified in 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 29927023, 31905448, internal lab contributors).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PP4			This variant was identified in a individuals with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (PMIDs: 31905448, 29927023, internal lab contributors)
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