

Variant: *NM_033508.3:c.973A>C*

Version: 1.0

CA367399833 [↗](#)

2664366 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 54f7636b-7d34-417d-86d3-149d6f4ad9d3

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HGVS expressions

NM_033508.3:c.973A>C

NC_000007.14:g.44146506T>G
CM000669.2:g.44146506T>G
NC_000007.13:g.44186105T>G
CM000669.1:g.44186105T>G
NC_000007.12:g.44152630T>G
NG_008847.1:g.47918A>C
NG_008847.2:g.56665A>C
ENST00000395796.8:c.*974A>C
ENST00000616242.5:c.*96A>C
ENST00000683378.1:n.202A>C
ENST00000345378.7:c.979A>C
ENST00000403799.8:c.976A>C
ENST00000671824.1:c.1039A>C
ENST00000673284.1:c.976A>C
ENST00000345378.6:c.979A>C
ENST00000395796.7:c.973A>C
ENST00000403799.7:c.976A>C
ENST00000437084.1:c.925A>C
ENST00000473353.1:n.274A>C
ENST00000616242.4:c.973A>C
NM_000162.3:c.976A>C
NM_033507.1:c.979A>C
NM_033508.1:c.973A>C
NM_000162.4:c.976A>C
NM_001354800.1:c.976A>C
NM_001354801.1:c.8+113A>C
NM_033507.2:c.979A>C
NM_033508.2:c.973A>C
NM_000162.5:c.976A>C
NM_033507.3:c.979A>C

Pathogenic

Met criteria codes **6**

PP1_Strong

PP4_Moderate

PS4_Moderate

PP2

PP3

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Monogenic Diabetes VCEP

The c.976A>C variant in the glucokinase gene, GCK, causes an amino acid change of threonine to proline at codon 326 (p.(Thr326Pro)) 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 0.822, 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 four unrelated individuals with hyperglycemia (PMID: 19564454, 31595705, internal lab contributors). One of these individuals had 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 contributor). This variant segregated with hyperglycemia, with six informative meioses in three families (PP1_Strong; internal lab contributors, PMID: 31595705). In summary, c.976A>C 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, approved 8/11/2023): PP4_Moderate, PP1_Strong, PP2, PP3, PM2_Supporting, PS4_Moderate.

Met criteria codes

PP1_Strong			This variant segregated with hyperglycemia, with 6 informative meioses in 3 families (PP1_Strong; internal lab contributors).
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 contributor).
PS4_Moderate			This variant was identified in four unrelated individuals with hyperglycemia (PMID: 19564454, 31595705, 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 0.822, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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Curation History 

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