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.421A>T

Version: 1.0

CA367402020

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0f36f4ba-0809-4f25-b936-8ba7abddb636
Approved on: 2024/12/2
Published on: 2024/12/2

HGVS expressions

NM_033508.3:c.421A>T
NC_000007.14:g.44151015T>A
CM000669.2:g.44151015T>A
NC_000007.13:g.44190614T>A
CM000669.1:g.44190614T>A
NC_000007.12:g.44157139T>A
NG_008847.1:g.43409A>T
NG_008847.2:g.52156A>T
ENST00000395796.8:c.*422A>T
ENST00000616242.5:c.424A>T
ENST00000682635.1:n.910A>T
ENST00000345378.7:c.427A>T
ENST00000403799.8:c.424A>T
ENST00000671824.1:c.424A>T
ENST00000673284.1:c.424A>T
ENST00000345378.6:c.427A>T
ENST00000395796.7:c.421A>T
ENST00000403799.7:c.424A>T
ENST00000437084.1:c.373A>T
ENST00000616242.4:c.421A>T
NM_000162.3:c.424A>T
NM_033507.1:c.427A>T
NM_033508.1:c.421A>T
NM_000162.4:c.424A>T
NM_001354800.1:c.424A>T
NM_033507.2:c.427A>T
NM_033508.2:c.421A>T
NM_000162.5:c.424A>T
NM_033507.3:c.427A>T

Pathogenic

Met criteria codes 3

PVS1 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS4

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.424A>T variant in the glucokinase gene, GCK, results in a premature termination at codon 142 (p.(Lys142Ter)) of NM_000162.5. This variant, located in biologically-relevant exon 4 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 2 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 33477506, MDEP internal lab contributor). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% persistently) (PP4_Moderate; internal lab contributor). In summary, c.424A>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, approved 8/11/2023): PVS1, PP4, PM2_Supporting.

Met criteria codes

PVS1	✔	This variant, located in biologically-relevant exon 4 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256).
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% persistently) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Absent from gnomAD v4.1

Not Met criteria codes

PS4	✖	This variant was identified in 2 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 33477506, MDEP internal lab contributor).

Curation History

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