

Variant: NM_001354803.2:c.356C>A

Version: 1.0

CA367397019 [↗](#)

2581124 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c2cfa5c9-fe78-486c-9a83-48d5221fa8c4

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HGVS expressions

NM_001354803.2:c.356C>A

NC_000007.14:g.44145212G>T

CM000669.2:g.44145212G>T

NC_000007.13:g.44184811G>T

CM000669.1:g.44184811G>T

NC_000007.12:g.44151336G>T

NG_008847.1:g.49212C>A

NG_008847.2:g.57959C>A

ENST00000395796.8:c.*1320C>A

ENST00000616242.5:c.*442C>A

ENST00000683378.1:n.548C>A

ENST00000336642.9:c.356C>A

ENST00000345378.7:c.1325C>A

ENST00000403799.8:c.1322C>A

ENST00000671824.1:c.1385C>A

ENST00000672743.1:n.334C>A

ENST00000673284.1:c.1322C>A

ENST00000336642.8:c.374C>A

ENST00000345378.6:c.1325C>A

ENST00000395796.7:c.1319C>A

ENST00000403799.7:c.1322C>A

ENST00000437084.1:c.1271C>A

ENST00000459642.1:n.702C>A

ENST00000616242.4:c.1319C>A

NM_000162.3:c.1322C>A

NM_033507.1:c.1325C>A

NM_033508.1:c.1319C>A

NM_000162.4:c.1322C>A

NM_001354800.1:c.1322C>A

NM_001354801.1:c.311C>A

NM_001354802.1:c.182C>A

NM_001354803.1:c.356C>A

NM_033507.2:c.1325C>A

NM_033508.2:c.1319C>A

NM_000162.5:c.1322C>A

NM_033507.3:c.1325C>A

NM_033508.3:c.1319C>A

Pathogenic

Met criteria codes 4

PP1_Strong

PS4_Moderate

PVS1

PM2_Supporting

Not Met criteria codes 1

PP4

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 1.2.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1322C>A variant in the glucokinase gene, GCK, results in a premature termination at codon 441 (p.(Ser441Ter)) of NM_000162.5. While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). This variant is absent in gnomAD (PM2_Supporting). This variant was identified in multiple individuals with diabetes/hyperglycemia consistent with GCK-MODY; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors). This variant was identified in 5 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID: 32710514, internal lab contributors). This variant segregated with diabetes, with 5 informative meioses in one family with MODY (PP1_Strong; internal lab contributors). In summary, the c.1322C>A variant 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): PVS1, PM2_Supporting, PS4_Moderate, PP1_strong.

Met criteria codes

PP1_Strong			5 meioses in one family
PS4_Moderate			This variant was identified in 5 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID: 32710514, internal lab contributors).
PVS1			While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1; 19790256).
PM2_Supporting			Absent in gnomAD

Not Met criteria codes

PP4			This variant was identified in multiple individuals with diabetes/hyperglycemia consistent with GCK-MODY; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors).
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Curation History

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