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Variant: NM_000162.5(GCK):c.1072C>T (p.Arg358Ter)

Version: 1.0

CA4239437

1803547 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 071ede73-ad78-43b1-899a-19a4115cb523
Approved on: 2025/6/27
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HGVS expressions

NM_000162.5:c.1072C>T
NM_000162.5(GCK):c.1072C>T (p.Arg358Ter)
NC_000007.14:g.44145678G>A
CM000669.2:g.44145678G>A
NC_000007.13:g.44185277G>A
CM000669.1:g.44185277G>A
NC_000007.12:g.44151802G>A
NG_008847.1:g.48746C>T
NG_008847.2:g.57493C>T
ENST00000395796.8:c.*1070C>T
ENST00000616242.5:c.*192C>T
ENST00000683378.1:n.298C>T
ENST00000336642.9:c.106C>T
ENST00000345378.7:c.1075C>T
ENST00000403799.8:c.1072C>T
ENST00000671824.1:c.1135C>T
ENST00000672743.1:n.84C>T
ENST00000673284.1:c.1072C>T
ENST00000336642.8:c.124C>T
ENST00000345378.6:c.1075C>T
ENST00000395796.7:c.1069C>T
ENST00000403799.7:c.1072C>T
ENST00000437084.1:c.1021C>T
ENST00000459642.1:n.452C>T
ENST00000473353.1:n.370C>T
ENST00000616242.4:c.1069C>T
NM_000162.3:c.1072C>T
NM_033507.1:c.1075C>T
NM_033508.1:c.1069C>T
NM_000162.4:c.1072C>T
NM_001354800.1:c.1072C>T
NM_001354801.1:c.61C>T
NM_001354802.1:c.-69C>T
NM_001354803.1:c.106C>T
NM_033507.2:c.1075C>T
NM_033508.2:c.1069C>T
NM_033507.3:c.1075C>T

NM_033508.3:c.1069C>T
NM_001354803.2:c.106C>T

Pathogenic

Met criteria codes 4

PVS1 PP4_Moderate
PM2_Supporting PS4_Moderate

Not Met criteria codes 1

PP1

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 2.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1072C>T variant in the glucokinase gene, GCK, results in a premature termination at codon 358 (p.(Arg358Ter)) of NM_000162.5. This variant, located in biologically-relevant exon 9 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 was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 38928025, internal lab contributors). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative) (PP4_Moderate; internal lab contributors). In summary, c.1072C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 2/17/2025): PVS1, PS4_Moderate, PM2_Supporting, PP4_Moderate.

Met criteria codes

PVS1	✔	This variant, located in biologically-relevant exon 9 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 (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs 10754480, 38928025, internal lab contributors).

Not Met criteria codes

PP1	✖	This variant segregated with diabetes with one informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (internal lab contributors).

Curation History

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