

Variant: NM_000162.5(GCK):c.1340_1368del (p.Arg447fs)

Version: 1.0

CA838788768 [↗](#)

1365679 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: b96f47ec-919b-43a2-95ae-64d916297c59

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HGVS expressions

NM_000162.5:c.1340_1368del

NM_000162.5(GCK):c.1340_1368del (p.Arg447fs)

NC_000007.14:g.44145172_44145200del

CM000669.2:g.44145172_44145200del

NC_000007.13:g.44184771_44184799del

CM000669.1:g.44184771_44184799del

NC_000007.12:g.44151296_44151324del

NG_008847.1:g.49230_49258del

NG_008847.2:g.57977_58005del

ENST00000395796.8:c.*1338_*1366del

ENST00000616242.5:c.*460_*488del

ENST00000683378.1:n.566_594del

ENST00000336642.9:c.374_402del

ENST00000345378.7:c.1343_1371del

ENST00000403799.8:c.1340_1368del

ENST00000671824.1:c.1403_1431del

ENST00000672743.1:n.352_380del

ENST00000673284.1:c.1340_1368del

ENST00000336642.8:c.392_420del

ENST00000345378.6:c.1343_1371del

ENST00000395796.7:c.1337_1365del

ENST00000403799.7:c.1340_1368del

ENST00000437084.1:c.1289_1317del

ENST00000459642.1:n.720_748del

ENST00000616242.4:c.1337_1365del

NM_000162.3:c.1340_1368del

NM_033507.1:c.1343_1371del

NM_033508.1:c.1337_1365del

NM_000162.4:c.1340_1368del

NM_001354800.1:c.1340_1368del

NM_001354801.1:c.329_357del

NM_001354802.1:c.200_228del

NM_001354803.1:c.374_402del

NM_033507.2:c.1343_1371del

NM_033508.2:c.1337_1365del

NM_033507.3:c.1343_1371del

NM_033508.3:c.1337_1365del

Pathogenic**Met criteria codes** 5

PS4

PP1_Strong

PP4

PM2_Supporting

PVS1

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.1340_1368del variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 447 (NM_000162.5), adding 2 novel amino acids before encountering a stop codon (p.(Arg447LeufsTer2)). 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 from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in at least 16 unrelated individuals who do not have autoimmune or absolute/near-absolute insulin-deficient diabetes (PS4; internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors). Additionally, this variant segregated with diabetes/hyperglycemia with 8 informative meioses in one family with MODY (PP1_Strong; internal lab contributor). Taken together, this evidence supports the classification of this variant as pathogenic for monogenic diabetes. ACMP/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PVS1, PP1_Strong, PS4, PP4, PM2_Supporting).

Met criteria codes**PS4**

This variant was identified in at least 16 unrelated individuals who do not have autoimmune or absolute/near-absolute insulin-deficient diabetes (PS4; internal lab contributors).

PP1_Strong

This variant segregated with diabetes/hyperglycemia, with 8 informative meioses in one family with MODY (PP1_Strong; internal lab contributor).

PP4

This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors).

PM2_Supporting

This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

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; PMID 19790256)

Curation History

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