

Variant: NM_001354803.2:c.365dup

Version: 1.0

CA2017997770 [↗](#)

2574161 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 1c703f03-c39d-4661-b412-ec75dd83011c

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HGVS expressions

NM_001354803.2:c.365dup

NC_000007.14:g.44145205dup
CM000669.2:g.44145205dup
NC_000007.13:g.44184804dup
CM000669.1:g.44184804dup
NC_000007.12:g.44151329dup
NG_008847.1:g.49221dup
NG_008847.2:g.57968dup
ENST00000395796.8:c.*1329dup
ENST00000616242.5:c.*451dup
ENST00000683378.1:n.557dup
ENST00000336642.9:c.365dup
ENST00000345378.7:c.1334dup
ENST00000403799.8:c.1331dup
ENST00000671824.1:c.1394dup
ENST00000672743.1:n.343dup
ENST00000673284.1:c.1331dup
ENST00000336642.8:c.383dup
ENST00000345378.6:c.1334dup
ENST00000395796.7:c.1328dup
ENST00000403799.7:c.1331dup
ENST00000437084.1:c.1280dup
ENST00000459642.1:n.711dup
ENST00000616242.4:c.1328dup
NM_000162.3:c.1331dup
NM_033507.1:c.1334dup
NM_033508.1:c.1328dup
NM_000162.4:c.1331dup
NM_001354800.1:c.1331dup
NM_001354801.1:c.320dup
NM_001354802.1:c.191dup
NM_001354803.1:c.365dup
NM_033507.2:c.1334dup
NM_033508.2:c.1328dup
NM_000162.5:c.1331dup
NM_033507.3:c.1334dup
NM_033508.3:c.1328dup

Likely Pathogenic

Met criteria codes 2

PM2_Supporting

PVS1

Not Met criteria codes 3

PS4

PP1

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.1331dup variant in the GCK gene causes a frameshift in the protein at codon 445 (NM_000162.5), adding 14 novel amino acids before encountering a stop codon (p.(Ser445GlnfsTer14)). While this variant, located in exon 10/10, is predicted to result in a premature stop codon that is predicted to escape nonsense mediated decay, it is a functionally important region in a gene where loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). Additionally, this variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in one individual with a clinical picture consistent with monogenic diabetes; however PS4_Moderate cannot be applied because this number is below the MDEP threshold (internal lab contributor). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors). This variant segregated with disease with one informative meiosis in a family with MODY; however, this does not meet the thresholds for PP1 set by Jarvik and Browning (PMID: 27236918) (internal lab contributor). In summary, c.1331dup meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0 approved 6/7/2023): PVS1, PM2_Supporting.

Met criteria codes

PM2_Supporting



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

PVS1



While this variant, located in exon 10/10, may cause a premature stop codon that is predicted to escape nonsense mediated decay, it is a functionally important region in a gene where loss-of-function is an established disease mechanism (PVS1)

Not Met criteria codes

PS4



This variant was identified in one individual with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold (internal lab contributor)

PP1



NOT MET: This variant segregated with disease with one informative meiosis in a family with MODY, however this does not meet the thresholds for PP1 set by Jarvik and Browning (PMID: 27236918) (internal lab contributor).

PP4



This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors).

Curation History [↗](#)

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