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_000162.5(GCK):c.1372_1373del (p.Lys458fs)

Version: 1.0

CA213762

36201 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 10f18a1f-a08b-4898-a7dc-f5dbf2c456e5
Approved on: 2023/9/1
Published on: 2023/9/1

HGVS expressions

NM_000162.5:c.1372_1373del
NM_000162.5(GCK):c.1372_1373del (p.Lys458fs)
NC_000007.14:g.44145161_44145162del
CM000669.2:g.44145161_44145162del
NC_000007.13:g.44184760_44184761del
CM000669.1:g.44184760_44184761del
NC_000007.12:g.44151285_44151286del
NG_008847.1:g.49262_49263del
NG_008847.2:g.58009_58010del
ENST00000395796.8:c.*1370_*1371del
ENST00000616242.5:c.*492_*493del
ENST00000683378.1:n.598_599del
ENST00000336642.9:c.406_407del
ENST00000345378.7:c.1375_1376del
ENST00000403799.8:c.1372_1373del
ENST00000671824.1:c.1435_1436del
ENST00000672743.1:n.381+3_381+4del
ENST00000673284.1:c.1369+3_1369+4del
ENST00000336642.8:c.424_425del
ENST00000345378.6:c.1375_1376del
ENST00000395796.7:c.1369_1370del
ENST00000403799.7:c.1372_1373del
ENST00000437084.1:c.1321_1322del
ENST00000459642.1:n.752_753del
ENST00000616242.4:c.1369_1370del
NM_000162.3:c.1372_1373del
NM_033507.1:c.1375_1376del
NM_033508.1:c.1369_1370del
NM_000162.4:c.1372_1373del
NM_001354800.1:c.1369+3_1369+4del
NM_001354801.1:c.361_362del
NM_001354802.1:c.229+3_229+4del
NM_001354803.1:c.406_407del
NM_033507.2:c.1375_1376del
NM_033508.2:c.1369_1370del
NM_033507.3:c.1375_1376del
NM_033508.3:c.1369_1370del

NM_001354803.2:c.406_407del

Likely Pathogenic

Met criteria codes 2

PM2_Supporting PVS1

Not Met criteria codes 3

PP1 PP4 PS4

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.1372_1373del variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 458 (NM_000162.6), adding 75 novel amino acids before encountering a stop codon (p.(Lys458GlufsTer75)). This variant, located in exon 10 of 10, is predicted to cause loss of a stop codon and result in an elongated protein. The additional residues are expected to cause improper folding, resulting in loss of function in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID 19790256). Additionally, this variant is absent in gnomAD v.2.1.1 (PM2_Supporting). This variant was identified in 2 unrelated individuals with a clinical picture consistent with non-autoimmune/insulin-deficient diabetes, however PS4 cannot be applied because this number is below the MDEP threshold (internal lab contributors). This variant was identified in a case consistent with GCK-hyperglycemia but there was insufficient clinical information to evaluate for PP4 (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 contributors). In summary, c.1372_1373del meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PVS1, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	Absent in gnomAD
PVS1	✔	This variant, located in exon 10 of 10, is predicted to cause loss of a stop codon and result in an elongated protein. The additional residues are expected to cause improper folding, resulting in loss of function in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID 19790256).

Not Met criteria codes

PP1	✖	One meiosis in a family
PP4	✖	Identified in a case consistent with GCK-MODY but insufficient clinical information to evaluate for PP4 (internal lab contributors).
PS4	✖	2 cases (internal contributors)

Curation History

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