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.1332del (p.Ser445fs)

Version: 1.0

CA213755

36197 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 1a6bc000-0c98-4f9c-bff7-53f1a4011d76
Approved on: 2023/6/20
Published on: 2023/6/20

HGVS expressions

NM_000162.5:c.1332del
NM_000162.5(GCK):c.1332del (p.Ser445fs)
NC_000007.14:g.44145202del
CM000669.2:g.44145202del
NC_000007.13:g.44184801del
CM000669.1:g.44184801del
NC_000007.12:g.44151326del
NG_008847.1:g.49222del
NG_008847.2:g.57969del
ENST00000395796.8:c.*1330del
ENST00000616242.5:c.*452del
ENST00000683378.1:n.558del
ENST00000336642.9:c.366del
ENST00000345378.7:c.1335del
ENST00000403799.8:c.1332del
ENST00000671824.1:c.1395del
ENST00000672743.1:n.344del
ENST00000673284.1:c.1332del
ENST00000336642.8:c.384del
ENST00000345378.6:c.1335del
ENST00000395796.7:c.1329del
ENST00000403799.7:c.1332del
ENST00000437084.1:c.1281del
ENST00000459642.1:n.712del
ENST00000616242.4:c.1329del
NM_000162.3:c.1332del
NM_033507.1:c.1335del
NM_033508.1:c.1329del
NM_000162.4:c.1332del
NM_001354800.1:c.1332del
NM_001354801.1:c.321del
NM_001354802.1:c.192del
NM_001354803.1:c.366del
NM_033507.2:c.1335del
NM_033508.2:c.1329del
NM_033507.3:c.1335del
NM_033508.3:c.1329del

NM_001354803.2:c.366del

Likely Pathogenic

Met criteria codes 2

PM2_Supporting PVS1

Not Met criteria codes 2

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.1332del variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 445 (NM_000162.5), adding 169 novel amino acids before encountering a stop codon (p.(Ser445ValfsTer169)). 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 from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in two unrelated individuals with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold, and PP4 could not be evaluated due to lack of clinical information (ClinVar ID 36197, internal lab contributor). In summary, the c.1332del variant 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	✔	Absent in gnomAD v2.1.1 (PM2_Supporting).
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

PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	One case from internal contributor, one case in ClinVar

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
⌑ Powered by BCM's Genboree.