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.1327G>T (p.Glu443Ter)

Version: 1.0

CA367396996

585915 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5409829d-3e29-4e50-b8ef-0cecc6917dee
Approved on: 2023/9/1
Published on: 2023/9/1

HGVS expressions

NM_000162.5:c.1327G>T
NM_000162.5(GCK):c.1327G>T (p.Glu443Ter)
NC_000007.14:g.44145207C>A
CM000669.2:g.44145207C>A
NC_000007.13:g.44184806C>A
CM000669.1:g.44184806C>A
NC_000007.12:g.44151331C>A
NG_008847.1:g.49217G>T
NG_008847.2:g.57964G>T
ENST00000395796.8:c.*1325G>T
ENST00000616242.5:c.*447G>T
ENST00000683378.1:n.553G>T
ENST00000336642.9:c.361G>T
ENST00000345378.7:c.1330G>T
ENST00000403799.8:c.1327G>T
ENST00000671824.1:c.1390G>T
ENST00000672743.1:n.339G>T
ENST00000673284.1:c.1327G>T
ENST00000336642.8:c.379G>T
ENST00000345378.6:c.1330G>T
ENST00000395796.7:c.1324G>T
ENST00000403799.7:c.1327G>T
ENST00000437084.1:c.1276G>T
ENST00000459642.1:n.707G>T
ENST00000616242.4:c.1324G>T
NM_000162.3:c.1327G>T
NM_033507.1:c.1330G>T
NM_033508.1:c.1324G>T
NM_000162.4:c.1327G>T
NM_001354800.1:c.1327G>T
NM_001354801.1:c.316G>T
NM_001354802.1:c.187G>T
NM_001354803.1:c.361G>T
NM_033507.2:c.1330G>T
NM_033508.2:c.1324G>T
NM_033507.3:c.1330G>T
NM_033508.3:c.1324G>T

NM_001354803.2:c.361G>T

Pathogenic

Met criteria codes 3

PVS1 PM2_Supporting PS4_Moderate

Not Met criteria codes 3

PM1 PS3 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.1327G>T variant in the glucokinase gene, GCK causes a premature stop codon in the protein at codon 443 (NM_000162.5). 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 was identified in 4 unrelated individuals with a clinical picture consistent with monogenic diabetes (PS4_Moderate; PMID: 20337973, PMID: 32901087, ClinVar ID 585915), including at least one individual with a clinical history suggestive of GCK-MODY but with insufficient clinical information provided to evaluate for PP4. In summary, c.1327G>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PVS1, PS4_Moderate, PM2_Supporting.

Met criteria codes

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).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in at least 4 unrelated individuals with with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID: 20337973, PMID: 32901087, ClinVar ID 585915).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	PMID: 32901087 found glucose binding and insulin secretion were decreased. No RAI and RSI calculated

PP4		✖	This variant was identified in individuals with a clinical history consistent with GCK-MODY, but there was insufficient information to evaluate for PP4.

Curation History

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