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_001354803.2:c.274A>T

Version: 1.0

CA367398252

2581128 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7e0be3b3-0dd3-4777-a4af-ba2e0a1b8750
Approved on: 2023/9/8
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HGVS expressions

NM_001354803.2:c.274A>T
NC_000007.14:g.44145510T>A
CM000669.2:g.44145510T>A
NC_000007.13:g.44185109T>A
CM000669.1:g.44185109T>A
NC_000007.12:g.44151634T>A
NG_008847.1:g.48914A>T
NG_008847.2:g.57661A>T
ENST00000395796.8:c.*1238A>T
ENST00000616242.5:c.*360A>T
ENST00000683378.1:n.466A>T
ENST00000336642.9:c.274A>T
ENST00000345378.7:c.1243A>T
ENST00000403799.8:c.1240A>T
ENST00000671824.1:c.1303A>T
ENST00000672743.1:n.252A>T
ENST00000673284.1:c.1240A>T
ENST00000336642.8:c.292A>T
ENST00000345378.6:c.1243A>T
ENST00000395796.7:c.1237A>T
ENST00000403799.7:c.1240A>T
ENST00000437084.1:c.1189A>T
ENST00000459642.1:n.620A>T
ENST00000616242.4:c.1237A>T
NM_000162.3:c.1240A>T
NM_033507.1:c.1243A>T
NM_033508.1:c.1237A>T
NM_000162.4:c.1240A>T
NM_001354800.1:c.1240A>T
NM_001354801.1:c.229A>T
NM_001354802.1:c.100A>T
NM_001354803.1:c.274A>T
NM_033507.2:c.1243A>T
NM_033508.2:c.1237A>T
NM_000162.5:c.1240A>T
NM_033507.3:c.1243A>T
NM_033508.3:c.1237A>T

Pathogenic

Met criteria codes 4

PVS1 PP1 PM2_Supporting PS4_Moderate

Not Met criteria codes 1

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.1240A>T variant in the glucokinase gene, GCK, results in a premature termination at codon 414 (p.(Lys414Ter)) of NM_000162.5. This variant, located in biologically-relevant exon 9 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). Additionally, this variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in four unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors). This variant segregated with diabetes, with two informative meioses in two families with MODY (PP1; internal lab contributors). There was insufficient clinical information on these individuals to evaluate for PP4 (internal lab contributors). In summary, c.1240A>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, PP4_Moderate, PP1, PM2_Supporting.

Met criteria codes

PVS1	✔	While this variant, located in exon 9 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).
PP1	✔	This variant segregated with diabetes, with two informative meioses in two families with MODY (PP1; internal lab contributors).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in four unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors).

Not Met criteria codes

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

Curation History

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