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.268G>A

Version: 1.0

CA367398289

3233994 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: d6254526-6b8f-4149-b3e0-81ed13994327
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HGVS expressions

NM_001354803.2:c.268G>A
NC_000007.14:g.44145516C>T
CM000669.2:g.44145516C>T
NC_000007.13:g.44185115C>T
CM000669.1:g.44185115C>T
NC_000007.12:g.44151640C>T
NG_008847.1:g.48908G>A
NG_008847.2:g.57655G>A
ENST00000395796.8:c.*1232G>A
ENST00000616242.5:c.*354G>A
ENST00000683378.1:n.460G>A
ENST00000336642.9:c.268G>A
ENST00000345378.7:c.1237G>A
ENST00000403799.8:c.1234G>A
ENST00000671824.1:c.1297G>A
ENST00000672743.1:n.246G>A
ENST00000673284.1:c.1234G>A
ENST00000336642.8:c.286G>A
ENST00000345378.6:c.1237G>A
ENST00000395796.7:c.1231G>A
ENST00000403799.7:c.1234G>A
ENST00000437084.1:c.1183G>A
ENST00000459642.1:n.614G>A
ENST00000616242.4:c.1231G>A
NM_000162.3:c.1234G>A
NM_033507.1:c.1237G>A
NM_033508.1:c.1231G>A
NM_000162.4:c.1234G>A
NM_001354800.1:c.1234G>A
NM_001354801.1:c.223G>A
NM_001354802.1:c.94G>A
NM_001354803.1:c.268G>A
NM_033507.2:c.1237G>A
NM_033508.2:c.1231G>A
NM_000162.5:c.1234G>A
NM_033507.3:c.1237G>A
NM_033508.3:c.1231G>A

Pathogenic

Met criteria codes 6

PM1 PM5_Strong PP4_Moderate PP2 PP3 PM2_Supporting

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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1234G>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to methionine at codon 412 (p.(Val412Met)) of NM_000162.5. GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.82, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 2 hour OGTT glucose increment < 3 mmol/L) (PP4_Moderate; internal lab contributors). Three other missense variants, c.1235T>A p.Val412Glu, c.1235T>C Val412Ala, and c.1235T>G Val412Gly have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong). In summary, c.1234G>A 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: PM5_Strong, PP4_Moderate, PM1, PP2, PP3, PM2_Supporting.

Met criteria codes

PM1	✔	This variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
PM5_Strong	✔	Three other missense variants, c.1235T>A p.Val412Glu, c.1235T>C Val412Ala, and c.1235T>G Val412Gly have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 2 hour OGTT glucose increment < 3 mmol/L) (PP4_Moderate; internal lab contributors).
PP2	✔	GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.82, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

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

Curation History

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