

Variant: NM_000162.5(GCK):c.1235T>G (p.Val412Gly)

Version: 1.0

CA367398280 [↗](#)

447387 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))
Condition: monogenic diabetes ([MONDO:0015967](#))
Inheritance Mode: Semidominant inheritance
UUID: bebc77b2-ec6d-4a20-8b26-a8fb9cdb636f
Approved on: 2024/4/27
Published on: 2024/4/27

HGVS expressions

NM_000162.5:c.1235T>G
NM_000162.5(GCK):c.1235T>G (p.Val412Gly)
NC_000007.14:g.44145515A>C
CM000669.2:g.44145515A>C
NC_000007.13:g.44185114A>C
CM000669.1:g.44185114A>C
NC_000007.12:g.44151639A>C
NG_008847.1:g.48909T>G
NG_008847.2:g.57656T>G
ENST00000395796.8:c.*1233T>G
ENST00000616242.5:c.*355T>G
ENST00000683378.1:n.461T>G
ENST00000336642.9:c.269T>G
ENST00000345378.7:c.1238T>G
ENST00000403799.8:c.1235T>G
ENST00000671824.1:c.1298T>G
ENST00000672743.1:n.247T>G
ENST00000673284.1:c.1235T>G
ENST00000336642.8:c.287T>G
ENST00000345378.6:c.1238T>G
ENST00000395796.7:c.1232T>G
ENST00000403799.7:c.1235T>G
ENST00000437084.1:c.1184T>G
ENST00000459642.1:n.615T>G
ENST00000616242.4:c.1232T>G
NM_000162.3:c.1235T>G
NM_033507.1:c.1238T>G
NM_033508.1:c.1232T>G
NM_000162.4:c.1235T>G
NM_001354800.1:c.1235T>G
NM_001354801.1:c.224T>G
NM_001354802.1:c.95T>G
NM_001354803.1:c.269T>G
NM_033507.2:c.1238T>G
NM_033508.2:c.1232T>G
NM_033507.3:c.1238T>G
NM_033508.3:c.1232T>G

Pathogenic**Met criteria codes** 7

PP4_Moderate PM5_Strong PP2
PP3 PM1 PS4_Moderate
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.1235T>G variant in the glucokinase gene, GCK, causes an amino acid change of valine to glycine at codon 412 (p.(Val412Gly)) 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 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 predicted to be deleterious by computational evidence, with a REVEL score of 0.99, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 34362814, 36939643, internal lab contributors). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). Two other missense variants, c.1235T>C p.Val412Ala and p.1235T>A p.Val412Glu, have been interpreted as pathogenic by the ClinGen MDEP, and p.Val412Gly has a greater Grantham distance than p.Val412Ala (PM5_Strong). In summary, c.1235T>G 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, approved 8/11/2023): PM5_Strong, PM1, PP2, PP3, PP4_Moderate, PS4_Moderate, PM2_Supporting.

Met criteria codes

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 negative antibodies) (PP4_Moderate; internal lab contributors).
PM5_Strong		✓	Two other missense variants, c.1235T>C p.Val412Ala and p.1235T>A p.Val412Glu have been interpreted as pathogenic by the ClinGen MDEP, and p.Val412Gly has a greater Grantham distance than p.Val412Ala (PM5_Strong).
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 0.99, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
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).

PS4_Moderate ⓘ ✓

This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 34362814, 36939643, internal lab contributors).

PM2_Supporting ⓘ ✓

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

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.