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Variant: NM_000162.5(GCK):c.1247A>C (p.His416Pro)

Version: 1.0

CA367398218

804839 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 691ec132-922e-4c15-bd8f-1a4f8dacd5ef
Approved on: 2026/1/7
Published on: 2026/1/28

HGVS expressions

NM_000162.5:c.1247A>C
NM_000162.5(GCK):c.1247A>C (p.His416Pro)
NC_000007.14:g.44145503T>G
CM000669.2:g.44145503T>G
NC_000007.13:g.44185102T>G
CM000669.1:g.44185102T>G
NC_000007.12:g.44151627T>G
NG_008847.1:g.48921A>C
NG_008847.2:g.57668A>C
ENST00000395796.8:c.*1245A>C
ENST00000616242.5:c.*367A>C
ENST00000683378.1:n.473A>C
ENST00000336642.9:c.281A>C
ENST00000345378.7:c.1250A>C
ENST00000403799.8:c.1247A>C
ENST00000671824.1:c.1310A>C
ENST00000672743.1:n.259A>C
ENST00000673284.1:c.1247A>C
ENST00000336642.8:c.299A>C
ENST00000345378.6:c.1250A>C
ENST00000395796.7:c.1244A>C
ENST00000403799.7:c.1247A>C
ENST00000437084.1:c.1196A>C
ENST00000459642.1:n.627A>C
ENST00000616242.4:c.1244A>C
NM_000162.3:c.1247A>C
NM_033507.1:c.1250A>C
NM_033508.1:c.1244A>C
NM_000162.4:c.1247A>C
NM_001354800.1:c.1247A>C
NM_001354801.1:c.236A>C
NM_001354802.1:c.107A>C
NM_001354803.1:c.281A>C
NM_033507.2:c.1250A>C
NM_033508.2:c.1244A>C
NM_033507.3:c.1250A>C
NM_033508.3:c.1244A>C

NM_001354803.2:c.281A>C

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PM1 PM5 PM2_Supporting

Not Met criteria codes 2

PS4 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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1247A>C variant in the glucokinase gene, GCK, causes an amino acid change of histidine to proline at codon 416 (p.His416Pro) of NM_000162.5. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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 0.99, which is greater than the MDEP VCEP threshold of 0.70 (PP3). The 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). Another missense variant at the same residue, c.1247A>G (p.His416Arg), has been classified as pathogenic by the ClinGen MDEP and p.His416Pro has a greater Grantham distance (PM5). This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold and PP4 cannot be applied due to insufficient clinical information (PMID: 17573900, 34556497; internal lab contributors). In summary, c.1247A>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PP2, PP3, PM1, PM2_Supporting, PM5.

Met criteria codes

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).
PM5	✔	Another missense variant at the same residue, c.1247A>G (p.His416Arg), has been classified as pathogenic by the ClinGen MDEP and p.His416Asp has a greater Grantham distance (PM5).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 17573900, 34556497; internal lab contributors).
PP4	✖	This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (PMID: 17573900, 34556497; internal lab contributors).

Curation History

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