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Variant: NM_000162.5(GCK):c.703A>G (p.Met235Val)

Version: 1.0

CA16605219

381599 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b377dbdf-2287-4e95-b027-fa8f8ace5de4
Approved on: 2025/9/17
Published on: 2025/9/26

HGVS expressions

NM_000162.5(GCK):c.703A>G (p.Met235Val)
NM_000162.5:c.703A>G
NC_000007.14:g.44147810T>C
CM000669.2:g.44147810T>C
NC_000007.13:g.44187409T>C
CM000669.1:g.44187409T>C
NC_000007.12:g.44153934T>C
NG_008847.1:g.46614A>G
NG_008847.2:g.55361A>G
ENST00000395796.8:c.*701A>G
ENST00000616242.5:c.703A>G
ENST00000345378.7:c.706A>G
ENST00000403799.8:c.703A>G
ENST00000671824.1:c.703A>G
ENST00000673284.1:c.703A>G
ENST00000345378.6:c.706A>G
ENST00000395796.7:c.700A>G
ENST00000403799.7:c.703A>G
ENST00000437084.1:c.652A>G
ENST00000616242.4:c.700A>G
NM_000162.3:c.703A>G
NM_033507.1:c.706A>G
NM_033508.1:c.700A>G
NM_000162.4:c.703A>G
NM_001354800.1:c.703A>G
NM_033507.2:c.706A>G
NM_033508.2:c.700A>G
NM_033507.3:c.706A>G
NM_033508.3:c.700A>G

Pathogenic

Met criteria codes 8

PM2_Supporting PP2 PP3 PS3_Moderate PP4_Moderate PS2 PS4 PP1_Strong

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Not Met criteria codes 1

PM1

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.703A>G variant in the glucokinase gene, GCK, causes an amino acid change of methionine to valine at codon 235 (p.(Met235Val)) 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 absent from gnomAD v4.1.0 (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.852, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Additionally, MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.45, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 17186219). This variant was identified in 15 unrelated individuals with hyperglycemia (PS4; PMID: 17186219, 24323243, 26552609, 31595705, 32086287; internal lab contributors). Furthermore, this variant segregated with hyperglycemia with 12 informative meioses in five families (PP1_Strong; PMID: 17186219, 31595705, 32086287; internal lab contributors). At least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT with minimal increment (<3mmol/L)) (PP4_Moderate; PMID: 17186219). This variant was identified as a de novo occurrence with confirmed parental relationships in an individual with a clinical picture consistent with GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6-7.6) (PS2; PMID: 24323243). In summary, c.703A>G meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.0.0, approved 7/23/2025): PS2, PS4, PP1_Strong, PS3_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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 0.852, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.45, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 17186219).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT with minimal increment (<3mmol/L)) (PP4_Moderate; PMID:17186219).
PS2	✔	This variant was identified as a de novo occurrence with confirmed parental relationships in an individual with a clinical picture consistent with GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6-7.6) (PS2; PMID: 24323243).
PS4	✔	This variant was identified in 15 unrelated individuals with hyperglycemia (PS4; PMID: 17186219, 24323243, 26552609, 31595705, 32086287; internal lab contributors).
PP1_Strong	✔	This variant segregated with hyperglycemia with 12 informative meioses in five families (PP1_Strong; PMID: 17186219, 31595705, 32086287; internal lab contributors).

Not Met criteria codes

PM1	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000162.5(GCK):c.703A>G (p.Met2…	Pathogenic	Monogenic Diabetes	2025-09-26	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.0.0	GCK

Showing 1 to 1 of 1 rows

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