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_033508.3:c.701T>G

Version: 1.0

CA367400741

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7dcbe174-95cc-49ef-92a3-d9d3bdac4f6b
Approved on: 2026/1/22
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HGVS expressions

NM_033508.3:c.701T>G
NC_000007.14:g.44147809A>C
CM000669.2:g.44147809A>C
NC_000007.13:g.44187408A>C
CM000669.1:g.44187408A>C
NC_000007.12:g.44153933A>C
NG_008847.1:g.46615T>G
NG_008847.2:g.55362T>G
ENST00000395796.8:c.*702T>G
ENST00000616242.5:c.704T>G
ENST00000345378.7:c.707T>G
ENST00000403799.8:c.704T>G
ENST00000671824.1:c.704T>G
ENST00000673284.1:c.704T>G
ENST00000345378.6:c.707T>G
ENST00000395796.7:c.701T>G
ENST00000403799.7:c.704T>G
ENST00000437084.1:c.653T>G
ENST00000616242.4:c.701T>G
NM_000162.3:c.704T>G
NM_033507.1:c.707T>G
NM_033508.1:c.701T>G
NM_000162.4:c.704T>G
NM_001354800.1:c.704T>G
NM_033507.2:c.707T>G
NM_033508.2:c.701T>G
NM_000162.5:c.704T>G
NM_033507.3:c.707T>G

Likely Pathogenic

Met criteria codes 4

PP2 PP3 PM5_Strong PM2_Supporting

Not Met criteria codes 3

PP4 PM1 PS4

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Evidence Links 0

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.704T>G variant in the glucokinase gene, GCK, causes an amino acid change of methionine to arginine at codon 235 (p.(Met235Arg)) 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 0.934, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Two other missense variants at the same residue, c.704T>C (p.Met235Thr) and c.703A>G (p.Met235Val), have been interpreted as pathogenic by the ClinGen MDEP, and p.Met235Arg has a greater Grantham distance than both of these variants (PM5_Strong). 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 (internal lab contributors). In summary, c.704T>G 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): PM5_Strong, PM2_Supporting, PP2, PP3.

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 0.934, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5_Strong	✔	Two other missense variants at the same residue, c.704T>C (p.Met235Thr) and c.703A>G (p.Met235Val), have been interpreted as pathogenic by the ClinGen MDEP, and p.Met235Arg has a greater Grantham distance than both variants (PM5_Strong).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

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 (internal lab contributors).
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant was identified in one individual with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).

Curation History

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