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Variant: NM_000162.5(GCK):c.787T>C (p.Ser263Pro)

Version: 1.0

CA152961

36258 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 9af40b37-5fda-4648-8252-561ce853763e
Approved on: 2025/6/27
Published on: 2025/6/27

HGVS expressions

NM_000162.5(GCK):c.787T>C (p.Ser263Pro)
NM_000162.5:c.787T>C
NC_000007.14:g.44147726A>G
CM000669.2:g.44147726A>G
NC_000007.13:g.44187325A>G
CM000669.1:g.44187325A>G
NC_000007.12:g.44153850A>G
NG_008847.1:g.46698T>C
NG_008847.2:g.55445T>C
ENST00000395796.8:c.*785T>C
ENST00000616242.5:c.787T>C
ENST00000345378.7:c.790T>C
ENST00000403799.8:c.787T>C
ENST00000671824.1:c.787T>C
ENST00000673284.1:c.787T>C
ENST00000345378.6:c.790T>C
ENST00000395796.7:c.784T>C
ENST00000403799.7:c.787T>C
ENST00000437084.1:c.736T>C
ENST00000616242.4:c.784T>C
NM_000162.3:c.787T>C
NM_033507.1:c.790T>C
NM_033508.1:c.784T>C
NM_000162.4:c.787T>C
NM_001354800.1:c.787T>C
NM_033507.2:c.790T>C
NM_033508.2:c.784T>C
NM_033507.3:c.790T>C
NM_033508.3:c.784T>C

Pathogenic

Met criteria codes 5

PS4 PP2 PP4_Moderate PM2_Supporting PP1_Strong

Not Met criteria codes 3

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS3 PP3 BP4

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 2.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.787T>C variant in the glucokinase gene, GCK, causes an amino acid change of serine to proline at codon 263 (p.(Ser263Pro)) of NM_000162.5. This variant was identified in at least 14 unrelated individuals with hyperglycemia (PS4; PMID: 32074423, internal lab contributors). This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 2.80e-7, which is below the threshold for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). This variant segregated with diabetes/hyperglycemia, with at least 21 informative meioses in 9 families (PP1_Strong; PMID: 32074423, internal lab contributors). 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 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 antibody negative) (PP4_Moderate; internal lab contributors). This variant has a REVEL score of 0.689, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function. The relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, and while the variant appears to result in thermal instability, the relative stability index was not calculated, therefore PS3_Supporting will not be applied (PMID: 16731834). In summary, c.787T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 2/17/2025): PS4, PM2_Supporting, PP1_Strong, PP2, PP4_Moderate.

Met criteria codes

PS4	✔	This variant was identified in at least 14 unrelated individuals with hyperglycemia (PS4; PMID 32074423, 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).
PP4_Moderate	✔	This variant was identified in multiple individuals with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID: 32074423, internal lab contributors)
PM2_Supporting	✔	This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 2.80e-7, which is below the threshold for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting).
PP1_Strong	✔	This variant segregated with hyperglycemia, with at least 21 informative meioses in nine families (PP1_Strong; PMID 32074423, internal lab contributors).

Not Met criteria codes

PS3	✖	The relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, and while the variant appears to result in thermal instability, the relative stability index was not calculated, therefore PS3_Supporting will not be

applied (PMID:16731834).

PP3		✖	This variant has a REVEL score of 0.689, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function.
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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