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Variant: NM_000162.5(GCK):c.830T>G (p.Val277Gly)

Version: 1.0

CA367400467

447422 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0234e9ae-b946-40ae-9528-ffc2837a885a
Approved on: 2026/2/24
Published on: 2026/2/26

HGVS expressions

NM_000162.5(GCK):c.830T>G (p.Val277Gly)
NM_000162.5:c.830T>G
NC_000007.14:g.44147683A>C
CM000669.2:g.44147683A>C
NC_000007.13:g.44187282A>C
CM000669.1:g.44187282A>C
NC_000007.12:g.44153807A>C
NG_008847.1:g.46741T>G
NG_008847.2:g.55488T>G
ENST00000395796.8:c.*828T>G
ENST00000616242.5:c.830T>G
ENST00000345378.7:c.833T>G
ENST00000403799.8:c.830T>G
ENST00000671824.1:c.830T>G
ENST00000673284.1:c.830T>G
ENST00000345378.6:c.833T>G
ENST00000395796.7:c.827T>G
ENST00000403799.7:c.830T>G
ENST00000437084.1:c.779T>G
ENST00000616242.4:c.827T>G
NM_000162.3:c.830T>G
NM_033507.1:c.833T>G
NM_033508.1:c.827T>G
NM_000162.4:c.830T>G
NM_001354800.1:c.830T>G
NM_033507.2:c.833T>G
NM_033508.2:c.827T>G
NM_033507.3:c.833T>G
NM_033508.3:c.827T>G

Likely Pathogenic

Met criteria codes 5

PP1 PP2 PP3 PP4_Moderate PM2_Supporting

Not Met criteria codes 2

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PM1 PS4

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.830T>G variant in the glucokinase gene, GCK, causes an amino acid change of valine to glycine at codon 277 (p.(Val277Gly)) 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 0.955, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (Internal lab contributors, MJM 2023 Case Report). Both of these individuals did have a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia with two informative meioses in two families (PP1; internal lab contributors, MJM 2023 Case Report). In summary, c.830T>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): PP1, PP4_Moderate, PP2, PP3, PM2_supporting.

Met criteria codes

PP1	✔	This variant segregated with hyperglycemia, with two informative meioses in two families (PP1; Internal lab contributors, MJM 2023 Case Report).
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 0.955, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and Three-generation, dominant family history of diabetes) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

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 two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen

MDEP threshold (PMID:24323243, internal lab contributors).

Curation History

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