

Variant: *NM_000162.5(GCK):c.185T>C (p.Val62Ala)*

Version: 2.0

CA367403278 [↗](#)

585917 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

UUID: 7ecf85fd-61ba-4385-8e7e-4ef8c9f464ec

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HGVS expressions

NM_000162.5:c.185T>C

NM_000162.5(GCK):c.185T>C (p.Val62Ala)

NC_000007.14:g.44153324A>G

CM000669.2:g.44153324A>G

NC_000007.13:g.44192923A>G

CM000669.1:g.44192923A>G

NC_000007.12:g.44159448A>G

NG_008847.1:g.41100T>C

NG_008847.2:g.49847T>C

ENST00000395796.8:c.*183T>C

ENST00000616242.5:c.185T>C

ENST00000682635.1:n.671T>C

ENST00000345378.7:c.188T>C

ENST00000403799.8:c.185T>C

ENST00000671824.1:c.185T>C

ENST00000673284.1:c.185T>C

ENST00000345378.6:c.188T>C

ENST00000395796.7:c.182T>C

ENST00000403799.7:c.185T>C

ENST00000437084.1:c.185T>C

ENST00000616242.4:c.182T>C

NM_000162.3:c.185T>C

NM_033507.1:c.188T>C

NM_033508.1:c.182T>C

NM_000162.4:c.185T>C

NM_001354800.1:c.185T>C

NM_033507.2:c.188T>C

NM_033508.2:c.182T>C

NM_033507.3:c.188T>C

NM_033508.3:c.182T>C

Pathogenic

Met criteria codes 7

- PS3_Moderate
- PP1_Strong
- PP4_Moderate
- PP2
- PP3
- PM5
- PM2_Supporting

Not Met criteria codes 1

- PS4

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 1.3.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.185T>C variant in the glucokinase gene, GCK, causes an amino acid change of valine to alanine at codon 62 (p.(Val62Ala)) 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 also predicted to be deleterious by computational evidence, with a REVEL score of 0.97, which is greater than the MDEP VCEP threshold of 0.70 (PP3). MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.23, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 16731834). This variant has an incomputable Popmax filtering allele frequency in gnomAD v2.1.1 due to 0 copies in the European non-Finnish subpopulation and 1 copy in the African subpopulation, below the ClinGen MDEP threshold for PM2_Supporting (Popmax FAF ≤0.000003 and ≤ 2 copies in ENF and ≤1 copy in any other subpopulation) (PM2_Supporting). It was identified in at least 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: 18399931, PMID: 9736233, ClinVar ID: 585917). One of these individuals has a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID: 18399931). This variant segregated with diabetes, with five informative meioses in one family with MODY (PP1_Strong; PMID: 9736233, internal lab contributors). Another missense variant, c.184G>A (p.Val62Met) has been interpreted as pathogenic by the ClinGen MDEP and p.Val62Ala has a greater Grantham distance (PM5). In summary, the c.185T>C variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PP4_Moderate, PP1_Strong, PM5, PS3_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PS3_Moderate			MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.23, which is below the MDEP cutoff (<0.5) (PMID: 16731834).
PP1_Strong			This variant segregated with diabetes, with five informative meioses in one family with MODY (PP1_Strong; PMID: 9736233).
PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID: 18399931).
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 0.97, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5			Another missense variant, c.184G>A (p.Val62Met) has been interpreted as pathogenic by the ClinGen MDEP and p.Val62Ala has a greater Grantham distance (PM5).
PM2_Supporting			This variant has an incomputable Popmax filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the African subpopulation, below the ClinGen MDEP threshold for PM2_Supporting (Popmax FAF ≤0.000003 and ≤ 2 copies in ENF and ≤1 copy in any other subpopulation) (PM2_Supporting).

Not Met criteria codes

PS4			This variant was identified in at least 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
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ClinGen MDEP threshold (PMID:18399931, PMID: 9736233, ClinVar ID: 585917).

Curation History

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