

Variant: NM_000162.5(GCK):c.1151C>T (p.Ala384Val)

Version: 1.0

CA367398721 [↗](#)

804836 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))
Condition: monogenic diabetes ([MONDO:0015967](#))
Inheritance Mode: Semidominant inheritance
UUID: 81727eb0-26ea-4013-84e2-f007ade17b2d
Approved on: 2025/6/6
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HGVS expressions

NM_000162.5:c.1151C>T
NM_000162.5(GCK):c.1151C>T (p.Ala384Val)
NC_000007.14:g.44145599G>A
CM000669.2:g.44145599G>A
NC_000007.13:g.44185198G>A
CM000669.1:g.44185198G>A
NC_000007.12:g.44151723G>A
NG_008847.1:g.48825C>T
NG_008847.2:g.57572C>T
ENST00000395796.8:c.*1149C>T
ENST00000616242.5:c.*271C>T
ENST00000683378.1:n.377C>T
ENST00000336642.9:c.185C>T
ENST00000345378.7:c.1154C>T
ENST00000403799.8:c.1151C>T
ENST00000671824.1:c.1214C>T
ENST00000672743.1:n.163C>T
ENST00000673284.1:c.1151C>T
ENST00000336642.8:c.203C>T
ENST00000345378.6:c.1154C>T
ENST00000395796.7:c.1148C>T
ENST00000403799.7:c.1151C>T
ENST00000437084.1:c.1100C>T
ENST00000459642.1:n.531C>T
ENST00000616242.4:c.1148C>T
NM_000162.3:c.1151C>T
NM_033507.1:c.1154C>T
NM_033508.1:c.1148C>T
NM_000162.4:c.1151C>T
NM_001354800.1:c.1151C>T
NM_001354801.1:c.140C>T
NM_001354802.1:c.11C>T
NM_001354803.1:c.185C>T
NM_033507.2:c.1154C>T
NM_033508.2:c.1148C>T
NM_033507.3:c.1154C>T
NM_033508.3:c.1148C>T

Likely Pathogenic

Met criteria codes 6

- PP4_Moderate
- PM2_Supporting
- PM5_Supporting
- PS4_Moderate
- PP2
- PP3

Not Met criteria codes 1

- PP1

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 2.0.0*
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1151C>T variant in the glucokinase gene, GCK, causes an amino acid change of alanine to valine at codon 384 (p.(Ala384Val)) 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 0.902, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 24735133, 30663027, 31576961, 36504295, internal lab contributors). Additionally, 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 negative autoantibodies) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, 24735133). Another missense variant at the same codon, c.1151C>A (p.Ala384Glu), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ala384Val (PM5_Supporting). In summary, c.1151C>T meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 2/17/2025): PS4_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3, PM5_Supporting.

Met criteria codes

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 negative autoantibodies) (PP4_Moderate; internal lab contributors).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5_Supporting			Another missense variant, c.1151C>A (p.Ala384Glu), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ala384Val (PM5_Supporting).
PS4_Moderate			This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 24735133, 30663027, 31576961, 36504295, 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).

PP3	 	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.902, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
Not Met criteria codes		
PP1	 	This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, 24735133).

Curation History 		
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