

Variant: NM_001354803.2:c.188G>T

Version: 1.0

CA367398710 [↗](#)

Gene: GCK ([HGNC:2645](#))
Condition: monogenic diabetes ([MONDO:0015967](#))
Inheritance Mode: Semidominant inheritance
UUID: 737bd9fe-8a84-4367-8b9d-369f4fb4c656
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HGVS expressions

NM_001354803.2:c.188G>T
NC_000007.14:g.44145596C>A
CM000669.2:g.44145596C>A
NC_000007.13:g.44185195C>A
CM000669.1:g.44185195C>A
NC_000007.12:g.44151720C>A
NG_008847.1:g.48828G>T
NG_008847.2:g.57575G>T
ENST00000395796.8:c.*1152G>T
ENST00000616242.5:c.*274G>T
ENST00000683378.1:n.380G>T
ENST00000336642.9:c.188G>T
ENST00000345378.7:c.1157G>T
ENST00000403799.8:c.1154G>T
ENST00000671824.1:c.1217G>T
ENST00000672743.1:n.166G>T
ENST00000673284.1:c.1154G>T
ENST00000336642.8:c.206G>T
ENST00000345378.6:c.1157G>T
ENST00000395796.7:c.1151G>T
ENST00000403799.7:c.1154G>T
ENST00000437084.1:c.1103G>T
ENST00000459642.1:n.534G>T
ENST00000616242.4:c.1151G>T
NM_000162.3:c.1154G>T
NM_033507.1:c.1157G>T
NM_033508.1:c.1151G>T
NM_000162.4:c.1154G>T
NM_001354800.1:c.1154G>T
NM_001354801.1:c.143G>T
NM_001354802.1:c.14G>T
NM_001354803.1:c.188G>T
NM_033507.2:c.1157G>T
NM_033508.2:c.1151G>T
NM_000162.5:c.1154G>T
NM_033507.3:c.1157G>T
NM_033508.3:c.1151G>T

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4 PM5_Supporting
PM2_Supporting

Not Met criteria codes 2

PP1 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 2.0.0
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1154G>T variant in the glucokinase gene, GCK, causes an amino acid change of glycine to valine at codon 385 (p.(Gly385Val)) 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 0.943, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 10588527, internal lab contributors). One of these individuals did have a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; PMID: 10588527). This variant was identified as a de novo occurrence with confirmed parental relationships in one individual with diabetes, but whose clinical picture is not highly specific for GCK-hyperglycemia (PS2_Moderate; internal lab contributors). Additionally, 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 (internal lab contributors). Another missense variant, c.1153G>A, p.Gly385Arg, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.1154G>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): PP2, PP3, PM2_supporting, PP4, PM5_supporting, PS2_Moderate.

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 0.943, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4		✓	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%) (PP4; PMID: 10588527).
PM5_Supporting		✓	Other missense variants at the same codon, c.1153G>A (p.Gly385Arg) and c.1153G>T (p.Gly385Trp), have been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
PM2_Supporting		✓	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

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 (internal lab contributors).
PS4			This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 10588527, internal lab contributors).

Curation History

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