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Variant: NM_001354803.2:c.187G>T

Version: 1.0

CA367398715

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 78a9d18d-8cb7-4db8-8b53-69085e267257
Approved on: 2025/6/2
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HGVS expressions

NM_001354803.2:c.187G>T
NC_000007.14:g.44145597C>A
CM000669.2:g.44145597C>A
NC_000007.13:g.44185196C>A
CM000669.1:g.44185196C>A
NC_000007.12:g.44151721C>A
NG_008847.1:g.48827G>T
NG_008847.2:g.57574G>T
ENST00000395796.8:c.*1151G>T
ENST00000616242.5:c.*273G>T
ENST00000683378.1:n.379G>T
ENST00000336642.9:c.187G>T
ENST00000345378.7:c.1156G>T
ENST00000403799.8:c.1153G>T
ENST00000671824.1:c.1216G>T
ENST00000672743.1:n.165G>T
ENST00000673284.1:c.1153G>T
ENST00000336642.8:c.205G>T
ENST00000345378.6:c.1156G>T
ENST00000395796.7:c.1150G>T
ENST00000403799.7:c.1153G>T
ENST00000437084.1:c.1102G>T
ENST00000459642.1:n.533G>T
ENST00000616242.4:c.1150G>T
NM_000162.3:c.1153G>T
NM_033507.1:c.1156G>T
NM_033508.1:c.1150G>T
NM_000162.4:c.1153G>T
NM_001354800.1:c.1153G>T
NM_001354801.1:c.142G>T
NM_001354802.1:c.13G>T
NM_001354803.1:c.187G>T
NM_033507.2:c.1156G>T
NM_033508.2:c.1150G>T
NM_000162.5:c.1153G>T
NM_033507.3:c.1156G>T
NM_033508.3:c.1150G>T

Likely Pathogenic

Met criteria codes 5

PM5_Supporting PM2_Supporting PP2 PP3 PP4_Moderate

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.1153G>T variant in the glucokinase gene, GCK, causes an amino acid change of glycine to tryptophan at codon 385 (p.(Gly385Trp)) 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 0.953, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD 4.1.0 (PM2_Supporting). 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 persistent impaired fasting glucose) (PP4_Moderate; PMID: 20337973). Another missense variant at the same codon, c.1153G>A (p.Gly385Arg), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.1153G>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_Moderate, PM5_supporting.

Met criteria codes

PM5_Supporting	✔	Another missense variant at the same codon, c.1153G>A (p.Gly385Arg), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.1.0: absent
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 0.953, 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 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and persistent impaired fasting glucose) (PP4_Moderate; PMID: 20337973).

Curation History

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