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Variant: NM_000162.5(GCK):c.1153G>A (p.Gly385Arg)

Version: 1.0

CA213721

36179 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 423d0c30-bcb7-448f-b5b4-eab03b3ba507
Approved on: 2025/6/2
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HGVS expressions

NM_000162.5:c.1153G>A
NM_000162.5(GCK):c.1153G>A (p.Gly385Arg)
NC_000007.14:g.44145597C>T
CM000669.2:g.44145597C>T
NC_000007.13:g.44185196C>T
CM000669.1:g.44185196C>T
NC_000007.12:g.44151721C>T
NG_008847.1:g.48827G>A
NG_008847.2:g.57574G>A
ENST00000395796.8:c.*1151G>A
ENST00000616242.5:c.*273G>A
ENST00000683378.1:n.379G>A
ENST00000336642.9:c.187G>A
ENST00000345378.7:c.1156G>A
ENST00000403799.8:c.1153G>A
ENST00000671824.1:c.1216G>A
ENST00000672743.1:n.165G>A
ENST00000673284.1:c.1153G>A
ENST00000336642.8:c.205G>A
ENST00000345378.6:c.1156G>A
ENST00000395796.7:c.1150G>A
ENST00000403799.7:c.1153G>A
ENST00000437084.1:c.1102G>A
ENST00000459642.1:n.533G>A
ENST00000616242.4:c.1150G>A
NM_000162.3:c.1153G>A
NM_033507.1:c.1156G>A
NM_033508.1:c.1150G>A
NM_000162.4:c.1153G>A
NM_001354800.1:c.1153G>A
NM_001354801.1:c.142G>A
NM_001354802.1:c.13G>A
NM_001354803.1:c.187G>A
NM_033507.2:c.1156G>A
NM_033508.2:c.1150G>A
NM_033507.3:c.1156G>A
NM_033508.3:c.1150G>A

NM_001354803.2:c.187G>A

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PS4 PP2 PP3 PM2_Supporting

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>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to arginine at codon 385 (p.(Gly385Arg)) 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 0.962, 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 at least seven unrelated individuals with hyperglycemia (PS4; internal lab contributors). 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 antibody negative) (PP4_Moderate; internal lab contributors). In summary, c.1153G>A 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, PS4, PP4_moderate.

Met criteria codes

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 antibody negative) (PP4_Moderate; internal lab contributors).
PS4	✔	This variant was identified in at least seven unrelated individuals with hyperglycemia (PS4; PMID: 19790256, ClinVar, 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 0.962, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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