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Variant: NM_033508.3:c.530G>T

Version: 1.0

CA367401649

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 2ba25ad4-e805-47e6-8995-9f8ad30d368a
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HGVS expressions

NM_033508.3:c.530G>T
NC_000007.14:g.44150015C>A
CM000669.2:g.44150015C>A
NC_000007.13:g.44189614C>A
CM000669.1:g.44189614C>A
NC_000007.12:g.44156139C>A
NG_008847.1:g.44409G>T
NG_008847.2:g.53156G>T
ENST00000395796.8:c.*531G>T
ENST00000616242.5:c.533G>T
ENST00000682635.1:n.1019G>T
ENST00000345378.7:c.536G>T
ENST00000403799.8:c.533G>T
ENST00000671824.1:c.533G>T
ENST00000673284.1:c.533G>T
ENST00000345378.6:c.536G>T
ENST00000395796.7:c.530G>T
ENST00000403799.7:c.533G>T
ENST00000437084.1:c.482G>T
ENST00000616242.4:c.530G>T
NM_000162.3:c.533G>T
NM_033507.1:c.536G>T
NM_033508.1:c.530G>T
NM_000162.4:c.533G>T
NM_001354800.1:c.533G>T
NM_033507.2:c.536G>T
NM_033508.2:c.530G>T
NM_000162.5:c.533G>T
NM_033507.3:c.536G>T

Likely Pathogenic

Met criteria codes 5

PM5 PM2_Supporting PP2 PP3 PP4_Moderate

Not Met criteria codes 3

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PM1 PS4 PP1

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.533G>T variant in the glucokinase gene, GCK, causes an amino acid change of glycine to valine at codon 178 (p.(Gly178Val)) 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 0.987, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v4.1 (PM2_Supporting). This variant was identified in three unrelated probands with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 36257325, internal lab contributors). At least 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% and OGTT with minimal increment <3mmol/L) (PP4_Moderate; Internal lab contributor). This variant segregated with hyperglycemia with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (Internal lab contributor). Another missense variant at the same residue, c.533G>A p.Gly178Glu, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gly178Val has a greater Grantham distance (PM5). In summary, c.533G>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 3.1.0, approved 10/10/2025): PP2, PP3, PM2_Supporting, PM5, PP4_Moderate.

Met criteria codes

PM5	✔	Another missense variant at the same residue, c.533G>A p.Gly178Glu, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gly178Val has a greater Grantham distance (PM5).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1 (PM2_Supporting).
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 0.987, 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 OGTT with minimal increment <3mmol/L) (PP4_Moderate; Internal lab contributor).

Not Met criteria codes

PM1	✖	This variant does not reside in an amino acid that directly binds glucose or ATP, which are defined as critical for the GCK protein's function by the ClinGen MDEP.

PS4		✖	This variant was identified in three unrelated probands with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 36257325, internal lab contributors).
PP1		✖	This variant segregated with hyperglycemia with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (Internal lab contributor).

Curation History

Showing 1 to 1 of 1 rows

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