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

Version: 1.0

CA367401650

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 1ef25737-db66-4cad-8e09-5c46e6dfc8d4
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HGVS expressions

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

Likely Pathogenic

Met criteria codes 6

PP4_Moderate PP1 PP2 PP3 PM5_Supporting PM2_Supporting

Not Met criteria codes 2

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS4 PM1

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>C variant in the glucokinase gene, GCK, causes an amnio acid change of glycine to alanine at codon 178 (p.(Gly178Ala)) 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 0.954, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1 and v4.1 (PM2_Supporting). This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 36257325, 29412391, 36504295). 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 negative antibodies) (PP4_Moderate; PMID:29412391). Additionally, this variant segregated with hyperglycemia, with 3 informative meioses in a single family (PP1; PMID: 29412391, 28012402). Another missense variant at the same residue, c.533G>A p.Gly178Glu, has been interpreted as pathogenic by the ClinGen MDEP, but has a greater Grantham distance than p.Gly178Ala (PM5_Supporting). In summary, c.533G>C 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): PP1, PM2_Supporting, PM5_Supporting, PP2, PP3, 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 negative antibodies) (PP4_Moderate; PMID:29412391)
PP1	✔	This variant segregated with hyperglycemia, with 3 informative meioses in a single family (PP1; PMID: 29412391, 28012402)
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 0.954, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5_Supporting	✔	Another missense variant, c.533G>A p.Gly178Glu, has been interpreted as pathogenic by the ClinGen MDEP,, but has a greater Grantham distance than p.Gly178Ala (PM5_Supporting).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1 and v4.1 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 36257325, 29412391, 36504295).

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.

Curation History

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