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Variant: NM_000162.5(GCK):c.533G>A (p.Gly178Glu)

Version: 1.0

CA10588428

265174 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 58340443-0eda-4023-b399-6eb7a888346b
Approved on: 2025/11/24
Published on: 2025/11/26

HGVS expressions

NM_000162.5:c.533G>A
NM_000162.5(GCK):c.533G>A (p.Gly178Glu)
NC_000007.14:g.44150015C>T
CM000669.2:g.44150015C>T
NC_000007.13:g.44189614C>T
CM000669.1:g.44189614C>T
NC_000007.12:g.44156139C>T
NG_008847.1:g.44409G>A
NG_008847.2:g.53156G>A
ENST00000395796.8:c.*531G>A
ENST00000616242.5:c.533G>A
ENST00000682635.1:n.1019G>A
ENST00000345378.7:c.536G>A
ENST00000403799.8:c.533G>A
ENST00000671824.1:c.533G>A
ENST00000673284.1:c.533G>A
ENST00000345378.6:c.536G>A
ENST00000395796.7:c.530G>A
ENST00000403799.7:c.533G>A
ENST00000437084.1:c.482G>A
ENST00000616242.4:c.530G>A
NM_000162.3:c.533G>A
NM_033507.1:c.536G>A
NM_033508.1:c.530G>A
NM_000162.4:c.533G>A
NM_001354800.1:c.533G>A
NM_033507.2:c.536G>A
NM_033508.2:c.530G>A
NM_033507.3:c.536G>A
NM_033508.3:c.530G>A

Pathogenic

Met criteria codes 6

PP4_Moderate PP1_Strong PS4 PP2 PP3 PM2_Supporting

Not Met criteria codes 1

PM1

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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.533G>A variant in the glucokinase gene, GCK, causes an amnio acid change of glycine to glutamic acid at codon 178 (p.(Gly178Glu)) of NM_000162.5. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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 0.964, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in at least 20 unrelated individuals with hyperglycemia (PMID: 25555642, 15928245, 30259503, 34556497, 29056535, 38054414, 19564454, 36257325, internal lab contributors) (PS4). This variant was identified in multiple individuals 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; internal lab contributors). This variant segregated with hyperglycemia, with at least 11 informative meioses in six families (PP1_Strong; PMID: 34556497, 36257325; internal lab contributors). In summary, c.533G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4, PM2_Supporting, PP2, PP3, PP4_Moderate, PP1_Strong

Met criteria codes

PP4_Moderate	✔	This variant was identified in multiple individuals 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; Internal lab contributors)
PP1_Strong	✔	This variant segregated with hyperglycemia, with at least 11 informative meioses in six families (PP1_Strong; PMID: 34556497, 36257325; Internal lab contributors).
PS4	✔	This variant was identified in at least 20 unrelated individuals with hyperglycemia (PS4 PMIDs: 36257325, 34556497, 30259503, 29056535; 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 0.964, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1 and v4.1.

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.

Curation History

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