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Variant: NM_000162.5(GCK):c.532G>A (p.Gly178Arg)

Version: 1.0

CA213798

36227 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e0c3c48e-9f0e-4d36-ab1c-010c4fe4aa9a
Approved on: 2026/3/22
Published on: 2026/3/26

HGVS expressions

NM_000162.5(GCK):c.532G>A (p.Gly178Arg)
NM_000162.5:c.532G>A
NC_000007.14:g.44150016C>T
CM000669.2:g.44150016C>T
NC_000007.13:g.44189615C>T
CM000669.1:g.44189615C>T
NC_000007.12:g.44156140C>T
NG_008847.1:g.44408G>A
NG_008847.2:g.53155G>A
ENST00000395796.8:c.*530G>A
ENST00000616242.5:c.532G>A
ENST00000682635.1:n.1018G>A
ENST00000345378.7:c.535G>A
ENST00000403799.8:c.532G>A
ENST00000671824.1:c.532G>A
ENST00000673284.1:c.532G>A
ENST00000345378.6:c.535G>A
ENST00000395796.7:c.529G>A
ENST00000403799.7:c.532G>A
ENST00000437084.1:c.481G>A
ENST00000616242.4:c.529G>A
NM_000162.3:c.532G>A
NM_033507.1:c.535G>A
NM_033508.1:c.529G>A
NM_000162.4:c.532G>A
NM_001354800.1:c.532G>A
NM_033507.2:c.535G>A
NM_033508.2:c.529G>A
NM_033507.3:c.535G>A
NM_033508.3:c.529G>A

Likely Pathogenic

Met criteria codes 6

PP2 PP3 PM5 PP4_Moderate PM2_Supporting PS4_Moderate

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.532G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to arginine at codon 178 (p.(Gly178Arg)) 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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v4.1 Grpmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and no copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 36257325,11508276; internal lab contributors). At least one of these individuals had 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 contributors). Another missense variant at the same residue, c.533G>A p.Gly178Glu, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gly178Arg has a greater Grantham distance (PM5). In summary, c.532G>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 3.1.0, approved 10/10/2025): PP2, PP3, PM2_Supporting, PM5, PP4_Moderate, PS4_Moderate.

Met criteria codes

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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5	✔	Another missense variant at the same residue, c.533G>A p.Gly178Glu, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gly178Arg has a greater Grantham distance (PM5).
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 contributors)
PM2_Supporting	✔	This variant has an incomputable gnomAD v4.1. Grpmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and no copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 36257325,11508276; internal lab contributors).

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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