The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000162.5(GCK):c.781G>A (p.Gly261Arg)

Version: 1.1

CA126211

16135 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 30f3b683-bd18-46bf-808d-e9059fa45ccb
Approved on: 2026/6/10
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HGVS expressions

NM_000162.5(GCK):c.781G>A (p.Gly261Arg)
NM_000162.5:c.781G>A
NC_000007.14:g.44147732C>T
CM000669.2:g.44147732C>T
NC_000007.13:g.44187331C>T
CM000669.1:g.44187331C>T
NC_000007.12:g.44153856C>T
NG_008847.1:g.46692G>A
NG_008847.2:g.55439G>A
ENST00000395796.8:c.*779G>A
ENST00000616242.5:c.781G>A
ENST00000345378.7:c.784G>A
ENST00000403799.8:c.781G>A
ENST00000671824.1:c.781G>A
ENST00000673284.1:c.781G>A
ENST00000345378.6:c.784G>A
ENST00000395796.7:c.778G>A
ENST00000403799.7:c.781G>A
ENST00000437084.1:c.730G>A
ENST00000616242.4:c.778G>A
NM_000162.3:c.781G>A
NM_033507.1:c.784G>A
NM_033508.1:c.778G>A
NM_000162.4:c.781G>A
NM_001354800.1:c.781G>A
NM_033507.2:c.784G>A
NM_033508.2:c.778G>A
NM_033507.3:c.784G>A
NM_033508.3:c.778G>A

Pathogenic

Met criteria codes 9

PM3 PP1_Strong PS3_Moderate PS2 PS4 PM2_Supporting PP2 PP3 PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Not Met criteria codes 1

PM1

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.781G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to arginine at codon 261 (p.(Gly261Arg)) 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 0.914, which is greater than the MDEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the "Other" subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF less than or equal to 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in more than 38 unrelated individuals with diabetes (PS4; PMIDs: 29417725, 33324081, 21518409, 25015100, 22611063, 17573900, internal lab contributors). This variant was identified in at least two 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 diabetes/hyperglycemia with 30 informative meioses in 18 families (PP1_Strong; PMID 33324081, 21518409, internal lab contributors). This variant was identified as a de novo occurrence with confirmed parental relationships in one individual with a clinical picture consistent with GCK-hyperglycemia (PS2; internal lab contributors). This variant has been detected in at least 2 individuals with neonatal diabetes who were both homozygous for the variant, confirmed in trans (PM3: PMID 33324081, 25015100, internal lab contributors). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Gly261Arg variant has a relative activity index (RAI) of 0.02, which is less than the MDEP VCEP threshold of 0.50 (PMID: 19903754). In summary, this variant meets the criteria to be classified as pathogenic for monogenic diabetews. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PM2_Supporting, PP2, PP3, PP4_Moderate, PS3_Moderate, PM3, PP1_Strong, PS4, PS2.

Met criteria codes

PM3	✔	This variant has been detected in at least 2 individuals with neonatal diabetes who were both homozygous for the variant, confirmed in trans (PM3: PMID 33324081, 25015100, internal lab contributors).
PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia with 30 informative meioses in 18 families (PP1_Strong; PMID 33324081, 21518409, internal lab contributors).
PS3_Moderate	✔	A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Gly261Arg variant has a relative activity index (RAI) of 0.02, which is less than the MDEP VCEP threshold of 0.50 (PMID: 19903754).
PS2	✔	This variant was identified as a de novo occurrence with confirmed parental relationships in one individual with a clinical picture consistent with GCK-hyperglycemia (PS2; internal lab contributors).
PS4	✔	This variant was identified in more than 38 unrelated individuals with diabetes /hyperglycemia (PS4; PMIDs: 29417725, 33324081, 21518409, 25015100, 22611063, 17573900, internal lab contributors).

PM2_Supporting		✔	This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the "Other" subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF less than or equal to 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (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 0.914, which is greater than the MDEP threshold of 0.70 (PP3).
PP4_Moderate		✔	This variant was identified in at least two 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).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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