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Variant: NM_000162.5(GCK):c.772G>A (p.Gly258Ser)

Version: 1.1

CA367400589

918070 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0e677f19-ff56-45e7-9d00-27e575269f2b
Approved on: 2026/4/28
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HGVS expressions

NM_000162.5:c.772G>A
NM_000162.5(GCK):c.772G>A (p.Gly258Ser)
NC_000007.14:g.44147741C>T
CM000669.2:g.44147741C>T
NC_000007.13:g.44187340C>T
CM000669.1:g.44187340C>T
NC_000007.12:g.44153865C>T
NG_008847.1:g.46683G>A
NG_008847.2:g.55430G>A
ENST00000395796.8:c.*770G>A
ENST00000616242.5:c.772G>A
ENST00000345378.7:c.775G>A
ENST00000403799.8:c.772G>A
ENST00000671824.1:c.772G>A
ENST00000673284.1:c.772G>A
ENST00000345378.6:c.775G>A
ENST00000395796.7:c.769G>A
ENST00000403799.7:c.772G>A
ENST00000437084.1:c.721G>A
ENST00000616242.4:c.769G>A
NM_000162.3:c.772G>A
NM_033507.1:c.775G>A
NM_033508.1:c.769G>A
NM_000162.4:c.772G>A
NM_001354800.1:c.772G>A
NM_033507.2:c.775G>A
NM_033508.2:c.769G>A
NM_033507.3:c.775G>A
NM_033508.3:c.769G>A

Pathogenic

Met criteria codes 9

PM1 PS3_Moderate PP1_Moderate PS4 PM5_Supporting PM2_Supporting PP2 PP3 PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

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.772G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to cysteine at codon 258 (p.(Gly258Ser)) 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 resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no more than one copy in any subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.993, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in at least 10 unrelated individuals with hyperglycemia (PS4; PMID: 36257325, 22035297, 33538814, internal lab contributors). Furthermore, at least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and multiple values of mild fasting hyperglycemia in PP4 range) (PP4_Moderate; PMID: 36257325, internal lab contributors). This variant segregated with hyperglycemia, with three informative meioses in two families with MODY (PP1_Moderate; PMID: 33538814, internal lab contributors). MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.01, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 41516031). Another missense variant at the same residue, c.773G>A (p.Gly258Asp), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Gly258Ser (PM5_Supporting). In summary, c.772G>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, PP1_Moderate, PM1, PS3_Moderate, PP4_Moderate, PP2, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

PM1	✔	This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.01, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 41516031).
PP1_Moderate	✔	This variant segregated with hyperglycemia, with three informative meioses in two families with MODY (PP1_Moderate; PMID: 33538814, internal lab contributors).
PS4	✔	This variant was identified in at least 10 unrelated individuals with hyperglycemia (PS4; PMID: 36257325, 22035297, 33538814, internal lab contributors)
PM5_Supporting	✔	Another missense variant at the same residue, c.773G>A (p.Gly258Asp), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Gly258Ser (PM5_Supporting).
PM2_Supporting	✔	This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no more than one copy in any subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (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 0.994, 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 (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and multiple values of mild fasting hyperglycemia in PP4 range) (PP4_Moderate; PMID: 36257325, internal lab contributors).

Curation History

Showing 1 to 2 of 2 rows

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