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Variant: NM_000162.5(GCK):c.773G>A (p.Gly258Asp)

Version: 1.0

CA4239526

972775 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 2aa1a35c-a1c2-4347-bdcb-f0637f9d9fec
Approved on: 2026/4/24
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HGVS expressions

NM_000162.5:c.773G>A
NM_000162.5(GCK):c.773G>A (p.Gly258Asp)
NC_000007.14:g.44147740C>T
CM000669.2:g.44147740C>T
NC_000007.13:g.44187339C>T
CM000669.1:g.44187339C>T
NC_000007.12:g.44153864C>T
NG_008847.1:g.46684G>A
NG_008847.2:g.55431G>A
ENST00000395796.8:c.*771G>A
ENST00000616242.5:c.773G>A
ENST00000345378.7:c.776G>A
ENST00000403799.8:c.773G>A
ENST00000671824.1:c.773G>A
ENST00000673284.1:c.773G>A
ENST00000345378.6:c.776G>A
ENST00000395796.7:c.770G>A
ENST00000403799.7:c.773G>A
ENST00000437084.1:c.722G>A
ENST00000616242.4:c.770G>A
NM_000162.3:c.773G>A
NM_033507.1:c.776G>A
NM_033508.1:c.770G>A
NM_000162.4:c.773G>A
NM_001354800.1:c.773G>A
NM_033507.2:c.776G>A
NM_033508.2:c.770G>A
NM_033507.3:c.776G>A
NM_033508.3:c.770G>A

Pathogenic

Met criteria codes 8

PM1 PP4_Moderate PP1_Strong PS3_Moderate PS4 PP2 PP3 PM2_Supporting

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Not Met criteria codes 1

PM5

Evidence Links 1

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.773G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to aspartate at codon 258 (p.(Gly258Asp)) 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 0.99, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMID: 36257325, 16444761, 34556497, internal lab contributors). Furthermore, at least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% detected incidentally in a pediatric patient and antibody negative) (PP4_Moderate; PMID: 16444761). This variant segregated with hyperglycemia, with four informative meioses in three families (PP1_Strong; PMID: 16444761, 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, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 41516031). Other missense variants at the same amino acid position have been classified as pathogenic (c.772G>A (p.Gly258Ser) and c.772G>T (p.Gly258Cys)); however, PM5 was not applied to avoid circularity as p.Gly258Asp contributed to the classification of the other variants at this residue. In summary, c.773G>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_Strong, PM1, PP4_Moderate, PP2, PP3, PM2_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).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% detected incidentally in a pediatric patient) (PP4_Moderate; PMID: 16444761).
PP1_Strong	✔	This variant segregated with hyperglycemia, with four informative meioses in three families (PP1; PMID: 16444761, internal lab contributors).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 41516031). RAI: 0 N/A, not available—for G258S, the affinity for glucose or ATP was so low that S0.5, ATP kM, Hill number, and kcat could not be measured, even at high substrate concentrations. PubMed:41516031
PS4	✔	This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMID: 36257325, 16444761, 34556497, 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 0.99, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
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).

Not Met criteria codes

PM5		✖	Other missense variants at the same amino acid position have been classified as pathogenic (c.772G>A (p.Gly258Ser) and c.772G>T (p.Gly258Cys)); however, PM5 was not applied to avoid circularity as p.Gly258Asp contributed to the classification of the other variants at this residue.

Curation History

Showing 1 to 1 of 1 rows

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