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Variant: NM_033508.3:c.761C>G

Version: 1.0

CA367400605

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e6a29588-16e6-42c6-b56d-d56b775bb409
Approved on: 2025/11/24
Published on: 2025/11/26

HGVS expressions

NM_033508.3:c.761C>G
NC_000007.14:g.44147749G>C
CM000669.2:g.44147749G>C
NC_000007.13:g.44187348G>C
CM000669.1:g.44187348G>C
NC_000007.12:g.44153873G>C
NG_008847.1:g.46675C>G
NG_008847.2:g.55422C>G
ENST00000395796.8:c.*762C>G
ENST00000616242.5:c.764C>G
ENST00000345378.7:c.767C>G
ENST00000403799.8:c.764C>G
ENST00000671824.1:c.764C>G
ENST00000673284.1:c.764C>G
ENST00000345378.6:c.767C>G
ENST00000395796.7:c.761C>G
ENST00000403799.7:c.764C>G
ENST00000437084.1:c.713C>G
ENST00000616242.4:c.761C>G
NM_000162.3:c.764C>G
NM_033507.1:c.767C>G
NM_033508.1:c.761C>G
NM_000162.4:c.764C>G
NM_001354800.1:c.764C>G
NM_033507.2:c.767C>G
NM_033508.2:c.761C>G
NM_000162.5:c.764C>G
NM_033507.3:c.767C>G

Pathogenic

Met criteria codes 7

PM2 PM1 PP4_Moderate PP1_Strong PP2 PP3 PS4_Moderate

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.764C>G variant in the glucokinase gene, GCK, causes an amino acid change of threonine to serine at codon 255 (p.(Thr255Ser)) of transcript NM_000162.5. 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 is absent from gnomAD v4.1.0 (PM2_Supporting). This variant segregated with hyperglycemia, with six informative meioses in four families (PP1_Strong; Internal lab contributors). This variant was identified in multiple individuals with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID 24808978, internal lab contributors). 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 0.714, which is greater than the MDEP VCEP threshold of 0.70 (PP3). In summary, c.764C>G 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): PM1, PM2_Supporting, PP2, PP3, PP4_Moderate, PS4_Moderate, PP1_Strong

Met criteria codes

PM2	✔	This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting).
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 multiple individuals with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 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 six informative meioses in four families (PP1_Strong; PMID: 24804978; 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 0.714, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4_Moderate	✔	This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 24808978, internal lab contributors).

Curation History

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