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Variant: NM_000162.5(GCK):c.763A>G (p.Thr255Ala)

Version: 1.0

CA367400608

2735005 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e4a05779-2d01-41ee-96a5-b471b87e9671
Approved on: 2025/11/24
Published on: 2025/11/26

HGVS expressions

NM_000162.5:c.763A>G
NM_000162.5(GCK):c.763A>G (p.Thr255Ala)
NC_000007.14:g.44147750T>C
CM000669.2:g.44147750T>C
NC_000007.13:g.44187349T>C
CM000669.1:g.44187349T>C
NC_000007.12:g.44153874T>C
NG_008847.1:g.46674A>G
NG_008847.2:g.55421A>G
ENST00000395796.8:c.*761A>G
ENST00000616242.5:c.763A>G
ENST00000345378.7:c.766A>G
ENST00000403799.8:c.763A>G
ENST00000671824.1:c.763A>G
ENST00000673284.1:c.763A>G
ENST00000345378.6:c.766A>G
ENST00000395796.7:c.760A>G
ENST00000403799.7:c.763A>G
ENST00000437084.1:c.712A>G
ENST00000616242.4:c.760A>G
NM_000162.3:c.763A>G
NM_033507.1:c.766A>G
NM_033508.1:c.760A>G
NM_000162.4:c.763A>G
NM_001354800.1:c.763A>G
NM_033507.2:c.766A>G
NM_033508.2:c.760A>G
NM_033507.3:c.766A>G
NM_033508.3:c.760A>G

Pathogenic

Met criteria codes 8

PM1 PM5 PP4_Moderate PP1_Strong PS4 PP2 PP3 PM2_Supporting

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.763A>G variant in the glucokinase gene, GCK, causes an amino acid change of threonine to alanine at codon 255 (p.(Thr255Ala)) of transcript 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 0.832, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting). This variant was identified in nine unrelated individuals with hyperglycemia (PS4; PMID 39504571, 25953829, 30259503, 17573900; internal lab contributors). Additionally, 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 negative antibodies) (PP4_Moderate; PMID: 25953829). This variant segregated with hyperglycemia with four informative meioses in three families (PP1_Strong; PMID: 17573900, internal lab contributors). 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). Another missense variant at the same residue, c.764C>G (p.Thr255Ser) has been interpreted as pathogenic by the ClinGen MDEP, and p.Thr255Ala has the same Grantham distance (PM5). In summary, c.763A>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): PS4, PP1_Strong, PM1, PM5, PM2_Supporting, PP2, PP3, PP4_Moderate.

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).
PM5	✓	Another missense variant at the same residue, c.764C>G (p.Thr255Ser) has been interpreted as pathogenic by the ClinGen MDEP, and p.Thr255Ala the same Grantham distance (PM5).
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 negative antibodies) (PP4_Moderate; PMID: 25953829).
PP1_Strong	✓	This variant segregated with hyperglycemia with four informative meioses in three families (PP1_Strong; PMID: 17573900, internal lab contributors).
PS4	✓	This variant was identified in nine unrelated individuals with hyperglycemia (PS4; PMID 39504571, 25953829, 30259503, 17573900; 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 0.832, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

PM2_Supporting		✔	This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting).

Curation History

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