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.748C>T (p.Arg250Cys)

Version: 1.0

CA16609268

393451 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5d160251-b40f-4a9f-8f75-1363fc23633c
Approved on: 2023/10/25
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HGVS expressions

NM_000162.5:c.748C>T
NM_000162.5(GCK):c.748C>T (p.Arg250Cys)
NC_000007.14:g.44147765G>A
CM000669.2:g.44147765G>A
NC_000007.13:g.44187364G>A
CM000669.1:g.44187364G>A
NC_000007.12:g.44153889G>A
NG_008847.1:g.46659C>T
NG_008847.2:g.55406C>T
ENST00000395796.8:c.*746C>T
ENST00000616242.5:c.748C>T
ENST00000345378.7:c.751C>T
ENST00000403799.8:c.748C>T
ENST00000671824.1:c.748C>T
ENST00000673284.1:c.748C>T
ENST00000345378.6:c.751C>T
ENST00000395796.7:c.745C>T
ENST00000403799.7:c.748C>T
ENST00000437084.1:c.697C>T
ENST00000616242.4:c.745C>T
NM_000162.3:c.748C>T
NM_033507.1:c.751C>T
NM_033508.1:c.745C>T
NM_000162.4:c.748C>T
NM_001354800.1:c.748C>T
NM_033507.2:c.751C>T
NM_033508.2:c.745C>T
NM_033507.3:c.751C>T
NM_033508.3:c.745C>T

Pathogenic

Met criteria codes 6

PM2_Supporting | PP2 | PP3 | PP4_Moderate | PS4 | PP1_Strong

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 1.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.748C>T variant in the glucokinase gene, GCK, causes an amino acid change of arginine to cysteine at codon 250 (p.(Arg250Cys)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). GCK: This variant was identified in 11 unrelated individuals with hyperglycemia (PS4; PMIDs: 30245511, 17204055, 19069349, internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L and 3 generation family history of diabetes/hyperglycemia (PP4_Moderate; internal lab contributors). This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in 2 families (PP1_Strong; PMID: 30245511, 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 0.944 which is greater than the MDEP VCEP threshold of 0.70 (PP3). In summary, c.748C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM2_Supporting, PS4, PP4_Moderate, PP1_Strong, PP2, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (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 0.944 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 (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L and 3 generation family history of diabetes/hyperglycemia (PP4_Moderate; internal lab contributors).
PS4	✔	GCK: This variant was identified in 11 unrelated individuals with hyperglycemia (PS4; PMIDs: 30245511, 17204055, 19069349, internal lab contributors).
PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in 2 families (PP1_Strong; PMID: 30245511, internal lab contributors).

Curation History

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