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.629T>C (p.Met210Thr)

Version: 1.0

CA367401300

804852 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 36ad32f3-6b33-4dae-8175-4a5daf06b61c
Approved on: 2024/1/18
Published on: 2024/1/18

HGVS expressions

NM_000162.5(GCK):c.629T>C (p.Met210Thr)
NM_000162.5:c.629T>C
NC_000007.14:g.44149810A>G
CM000669.2:g.44149810A>G
NC_000007.13:g.44189409A>G
CM000669.1:g.44189409A>G
NC_000007.12:g.44155934A>G
NG_008847.1:g.44614T>C
NG_008847.2:g.53361T>C
ENST00000395796.8:c.*627T>C
ENST00000616242.5:c.629T>C
ENST00000682635.1:n.1115T>C
ENST00000345378.7:c.632T>C
ENST00000403799.8:c.629T>C
ENST00000671824.1:c.629T>C
ENST00000673284.1:c.629T>C
ENST00000345378.6:c.632T>C
ENST00000395796.7:c.626T>C
ENST00000403799.7:c.629T>C
ENST00000437084.1:c.578T>C
ENST00000616242.4:c.626T>C
NM_000162.3:c.629T>C
NM_033507.1:c.632T>C
NM_033508.1:c.626T>C
NM_000162.4:c.629T>C
NM_001354800.1:c.629T>C
NM_033507.2:c.632T>C
NM_033508.2:c.626T>C
NM_033507.3:c.632T>C
NM_033508.3:c.626T>C

Pathogenic

Met criteria codes 6

PS4 PP2 PP3 PM2_Supporting PP1_Strong PS3_Supporting

Not Met criteria codes 1

PP4

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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.629T>C variant in the glucokinase gene, GCK, causes an amino acid change of methionine to threonine at codon 210 (p.(Met210Thr)) 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 is predicted to be deleterious by computational evidence, with a REVEL score of 0.982, which is greater than the MDEP threshold of 0.70 (PP3). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, but the wild-type ATP Km is not between 0.4-0.65, and the p.Met210Thr has Kcat/S0.5<0.5 (PS3_Supporting; PMID: 14517946, DOI:10.1007/s001250051289). This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency of due to 0 copies observed in the European non-Finnish population and only 1 copy in another subpopulation (Latino/admixed), thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting). This variant was identified in 11 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 25555642, 9049484, ClinVar ID: 804852, internal lab contributor). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributor). This variant segregated with diabetes, with 5 informative meioses in 2 families with MODY (PP1_Strong; internal lab contributors). Taken together, the evidence supports the classification of c.629T>C as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PP1_Strong, PS4, PS3_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PS4	✔	This variant was identified in 11 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 25555642, 9049484, ClinVar ID: 804852, internal lab contributor).
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 0.982, which is greater than the MDEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency of due to 0 copies observed in the European non-Finnish population and only 1 copy in another subpopulation (Latino/admixed), thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting).
PP1_Strong	✔	This variant segregated with diabetes, with 5 informative meioses in 2 families with MODY (PP1_Strong; internal lab contributors).
PS3_Supporting	✔	A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, but the wild-type ATP Km is not between 0.4-0.65, and the p.Met210Thr has Kcat/S0.5<0.5 (PS3_Supporting; PMID: 14517946, DOI:10.1007/s001250051289).

Not Met criteria codes

PP4	✖	This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributor).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.