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Variant: NM_000162.5(GCK):c.823C>T (p.Arg275Cys)

Version: 1.0

CA4239519

585927 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 10a41ed2-a058-4df3-b3ec-335ec9c2b90e
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HGVS expressions

NM_000162.5(GCK):c.823C>T (p.Arg275Cys)
NM_000162.5:c.823C>T
NC_000007.14:g.44147690G>A
CM000669.2:g.44147690G>A
NC_000007.13:g.44187289G>A
CM000669.1:g.44187289G>A
NC_000007.12:g.44153814G>A
NG_008847.1:g.46734C>T
NG_008847.2:g.55481C>T
ENST00000395796.8:c.*821C>T
ENST00000616242.5:c.823C>T
ENST00000345378.7:c.826C>T
ENST00000403799.8:c.823C>T
ENST00000671824.1:c.823C>T
ENST00000673284.1:c.823C>T
ENST00000345378.6:c.826C>T
ENST00000395796.7:c.820C>T
ENST00000403799.7:c.823C>T
ENST00000437084.1:c.772C>T
ENST00000616242.4:c.820C>T
NM_000162.3:c.823C>T
NM_033507.1:c.826C>T
NM_033508.1:c.820C>T
NM_000162.4:c.823C>T
NM_001354800.1:c.823C>T
NM_033507.2:c.826C>T
NM_033508.2:c.820C>T
NM_033507.3:c.826C>T
NM_033508.3:c.820C>T

Pathogenic

Met criteria codes 6

PP4_Moderate PS4 PP1 PP2 PP3 PM2_Supporting

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS3

Evidence Links 0

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.823C>T variant in the glucokinase gene, GCK, causes an amino acid change of arginine to cysteine at codon 275 (p.(Arg275Cys)) of NM_000162.5. This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMID: 24001579, internal lab contributors). This variant was identified in two individuals 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) (internal lab contributors). This variant segregated with diabetes/hyperglycemia, with 3 informative meioses in 1 family (PP1; PMID: 24001579). 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 0.901, which is greater than the MDEP VCEP threshold of 0.70 (PP3). While a study exploring the effect of this variant on protein function has been performed and suggests a possible impact on stability and dimerization, the study does not meet the criteria set forth by the MDEP for the application of PS3 or BS3 (PMID: 24001579). This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 1 copy in the European non-Finnish subpopulation, 1 copy in the African/African American subpopulation, and 1 copy in the South Asian subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF less than or equal to 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). In summary, 823C>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): PS4, PP4_Moderate, PP1, PP2, PP3, PM2_Supporting.

Met criteria codes

PP4_Moderate	✔	This variant was identified in two individuals 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) (internal lab contributors).
PS4	✔	This variant was identified in 7 unrelated individuals with hyperglycemia (PS4; PMIDs: 24001579, internal lab contributors).
PP1	✔	This variant segregated with diabetes, with 3 informative meioses in 1 family with MODY (PP1; PMID: 24001579).
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 0.901, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 1 copy in the European non-Finnish subpopulation, 1 copy in the African/African American subpopulation, and 1 copy in the South Asian subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF less than or equal to 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).

Not Met criteria codes

PS3	✖	While a study exploring the effect of this variant on protein function has been performed and suggests a possible impact on stability and dimerization, the study does not meet the criteria set forth by the MDEP for the application of PS3 or BS3 (PMID: 24001579).

Curation History

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