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Variant: NM_000162.5(GCK):c.127C>T (p.Arg43Cys)

Version: 1.0

CA367403451

585911 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 8eefadd2-11eb-46d6-88b2-35a21909f993
Approved on: 2023/8/13
Published on: 2023/8/13

HGVS expressions

NM_000162.5:c.127C>T
NM_000162.5(GCK):c.127C>T (p.Arg43Cys)
NC_000007.14:g.44153382G>A
CM000669.2:g.44153382G>A
NC_000007.13:g.44192981G>A
CM000669.1:g.44192981G>A
NC_000007.12:g.44159506G>A
NG_008847.1:g.41042C>T
NG_008847.2:g.49789C>T
ENST00000395796.8:c.*125C>T
ENST00000616242.5:c.127C>T
ENST00000682635.1:n.613C>T
ENST00000345378.7:c.130C>T
ENST00000403799.8:c.127C>T
ENST00000671824.1:c.127C>T
ENST00000673284.1:c.127C>T
ENST00000345378.6:c.130C>T
ENST00000395796.7:c.124C>T
ENST00000403799.7:c.127C>T
ENST00000437084.1:c.127C>T
ENST00000616242.4:c.124C>T
NM_000162.3:c.127C>T
NM_033507.1:c.130C>T
NM_033508.1:c.124C>T
NM_000162.4:c.127C>T
NM_001354800.1:c.127C>T
NM_033507.2:c.130C>T
NM_033508.2:c.124C>T
NM_033507.3:c.130C>T
NM_033508.3:c.124C>T

Pathogenic

Met criteria codes 8

PM5 PP1_Strong PS3_Moderate PS4 PM2_Supporting PP2 PP3 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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.127C>T variant in the glucokinase gene, GCK, causes an amino acid change of arginine to cysteine at codon 43 (p.(Arg43Cys)) 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 0.924, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Additionally, established functional studies demonstrated the p.Arg43Cys protein has a relative activity index (RAI) < 0.5, indicating that this variant impacts protein function (PS3_Moderate; PMID: 25015100). This variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in at least eight unrelated individuals with hyperglycemia/diabetes (PS4; PMIDs: 30592380, 21348868, PMID 23771172, 25015100). One of these individuals was homozygous for c.127C>T and had permanent neonatal diabetes mellitus (PNDM) and negative testing for ABCC8, KCNJ11, INS and EIF2AK3 (PP4; PMID 25015100). This variant also segregated with diabetes/hyperglycemia, with 5 informative meioses in one family (PP1_Strong; PMID 21348868). Another missense variant, c.128G>A (p.Arg43His), has been interpreted as pathogenic by the ClinGen MDEP and p.Arg43Cys has a greater Grantham distance (PM5). Taken together, this evidence supports the classification of this variant as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_Strong, PS4, PM5, PP2, PP3, PP4, PM2_Supporting, PS3_Moderate.

Met criteria codes

PM5 ✔	Another missense variant, c.128G>A (p.Arg43His) has been interpreted as pathogenic by the ClinGen MDEP and p.Arg43Cys has a greater Grantham distance (PM5).
PP1_Strong ✔	This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in at least one family (PP1_Strong; PMID 21348868).
PS3_Moderate ✔	Established functional studies demonstrated the p.Arg43Cys protein has a relative activity index < 0.5, indicating that this variant impacts protein function (PMID: 25015100).
PS4 ✔	This variant was identified in at least seven unrelated individuals with hyperglycemia (PS4; PMID 30592380, PMID 21348868, PMID 23771172, 25015100).
PM2_Supporting ✔	This variant is absent in 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 0.924, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4		✔	This variant was identified in the homozygous state in an individual with permanent neonatal diabetes mellitus (PNDM) and negative testing for ABCC8, KCNJ11, INS and EIF2AK3 (PP4; PMID 25015100).

Curation History

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