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Variant: NM_000162.5(GCK):c.571C>T (p.Arg191Trp)

Version: 1.0

CA367401530

426122 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: c6d46289-9537-46e1-99aa-e854f39affb2
Approved on: 2023/7/23
Published on: 2023/7/23

HGVS expressions

NM_000162.5(GCK):c.571C>T (p.Arg191Trp)
NM_000162.5:c.571C>T
NC_000007.14:g.44149977G>A
CM000669.2:g.44149977G>A
NC_000007.13:g.44189576G>A
CM000669.1:g.44189576G>A
NC_000007.12:g.44156101G>A
NG_008847.1:g.44447C>T
NG_008847.2:g.53194C>T
ENST00000395796.8:c.*569C>T
ENST00000616242.5:c.571C>T
ENST00000682635.1:n.1057C>T
ENST00000345378.7:c.574C>T
ENST00000403799.8:c.571C>T
ENST00000671824.1:c.571C>T
ENST00000673284.1:c.571C>T
ENST00000345378.6:c.574C>T
ENST00000395796.7:c.568C>T
ENST00000403799.7:c.571C>T
ENST00000437084.1:c.520C>T
ENST00000616242.4:c.568C>T
NM_000162.3:c.571C>T
NM_033507.1:c.574C>T
NM_033508.1:c.568C>T
NM_000162.4:c.571C>T
NM_001354800.1:c.571C>T
NM_033507.2:c.574C>T
NM_033508.2:c.568C>T
NM_033507.3:c.574C>T
NM_033508.3:c.568C>T

Pathogenic

Met criteria codes 7

PS2_Moderate PP4_Moderate PP1_Strong PS4 PP2 PP3 PM2_Supporting

Not Met criteria codes 1

PS3

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 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.571C>T variant in the glucokinase gene, GCK causes an amino acid change of Arg to Trp at codon 191 (p.(Arg191Trp)) 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 also predicted to be deleterious by computational evidence, with a REVEL score of 0.936, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable Popmax filtering allele frequency in gnomAD v2.1 due to only one copy in European non-Finnish population and one copy in another subpopulation, which is less than the MDEP threshold for PM2_Supporting (Popmax filtering FAF <= 0.000003 and <= 2 copies in ENF and ≤1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in more than 100 unrelated individuals with diabetes/hyperglycemia (PS4; PMIDs: 10753050, 22060211, 23295292, 28170077, internal lab contributors). This variant segregated with diabetes with at least 72 informative meioses from 51 families with MODY (PP1_Strong; internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID: 23295292). This variant was found de novo in an individual with a phenotype highly specific for GCK-MODY with unconfirmed parental relationships (PS2_Moderate; internal lab contributor). Functional studies demonstrated the p.Arg191Trp protein has RAI<0.5; however, the wild-type kinetic parameters didn't pass the quality control, and the PS3 cannot be applied (PMID: 30592380). In summary, this variant meets the criteria to be classified as Pathogenic for GCK-MODY. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2, approved 6/7/2023): PS4, PP1_Strong, PS2_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3.

Met criteria codes

PS2_Moderate	✔	This variant was found de novo in an individual with a phenotype highly specific for GCK-MODY with unconfirmed parental relationships (PS2_Moderate; internal lab contributor).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history of GCK-MODY (MODY probability calculator result >50%, and negative antibody) (PP4_Moderate; internal lab contributors).
PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia with at least 72 informative meioses from 51 families with MODY (PP1_Strong; internal lab contributors).
PS4	✔	This variant was identified in more than 100 unrelated individuals with diabetes/hyperglycemia (PS4; PMIDs: 10753050, 22060211, 23295292, 28170077, 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 0.936, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting		✔	This variant has an incomputable Popmax filtering allele frequency in gnomAD v2.1 due to only one copy in European non-Finnish population and one copy in another subpopulation, which is less than the MDEP threshold for PM2_Supporting (Popmax filtering FAF <= 0.000003 and <= 2 copies in ENF and ≤1 copy in any other subpopulation) (PM2_Supporting).

Not Met criteria codes

PS3		✖	Functional studies demonstrated the p.Arg191Trp protein has RAI<0.5; however, the wild-type kinetic parameters didn’t pass the quality control, and the PS3 cannot be applied (PMID: 30592380).

Curation History

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