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Variant: NM_000162.5(GCK):c.1190G>T (p.Arg397Leu)

Version: 1.0

CA341587

21077 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: ca025555-c2e2-4b53-9af7-3bdcb6aa5da7
Approved on: 2023/7/16
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HGVS expressions

NM_000162.5:c.1190G>T
NM_000162.5(GCK):c.1190G>T (p.Arg397Leu)
NC_000007.14:g.44145560C>A
CM000669.2:g.44145560C>A
NC_000007.13:g.44185159C>A
CM000669.1:g.44185159C>A
NC_000007.12:g.44151684C>A
NG_008847.1:g.48864G>T
NG_008847.2:g.57611G>T
ENST00000395796.8:c.*1188G>T
ENST00000616242.5:c.*310G>T
ENST00000683378.1:n.416G>T
ENST00000336642.9:c.224G>T
ENST00000345378.7:c.1193G>T
ENST00000403799.8:c.1190G>T
ENST00000671824.1:c.1253G>T
ENST00000672743.1:n.202G>T
ENST00000673284.1:c.1190G>T
ENST00000336642.8:c.242G>T
ENST00000345378.6:c.1193G>T
ENST00000395796.7:c.1187G>T
ENST00000403799.7:c.1190G>T
ENST00000437084.1:c.1139G>T
ENST00000459642.1:n.570G>T
ENST00000616242.4:c.1187G>T
NM_000162.3:c.1190G>T
NM_033507.1:c.1193G>T
NM_033508.1:c.1187G>T
NM_000162.4:c.1190G>T
NM_001354800.1:c.1190G>T
NM_001354801.1:c.179G>T
NM_001354802.1:c.50G>T
NM_001354803.1:c.224G>T
NM_033507.2:c.1193G>T
NM_033508.2:c.1187G>T
NM_033507.3:c.1193G>T
NM_033508.3:c.1187G>T

NM_001354803.2:c.224G>T

Pathogenic

Met criteria codes 8

PM3 PP4_Moderate PP1_Strong PS3_Moderate PS4 PP2 PP3 PM2_Supporting

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.1190G>T variant in the glucokinase gene, GCK, causes an amino acid change of Arg to Leu at codon 397 (p.(Arg397Leu)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 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 0.925 which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in 21 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID:17186219 , internal lab contributors). This variant segregated with diabetes, with at least 7 informative meioses in 14 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, HbA1c 5.6 - 7.6%, and OGTT increment < 3 mmol/L) (PP4_Moderate; PMID:17186219). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Arg397Leu has RAI=0.72, which is less than the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID 17186219). This variant has been detected in the homozygous state in at least 5 individuals with neonatal diabetes (PM3; internal lab contributors). In summary, c.1190G>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PM2_Supporting, PP2, PP3, PS4, PP1_Strong, PP4_Moderate, PS3_Supporting, PM3.

Met criteria codes

PM3	✔	This variant has been detected in at least 5 individuals with neonatal diabetes. Of those individuals, 5 were homozygous. (PM3; internal lab contributors).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L, HbA1c 5.6 - 7.6%, and OGTT increment < 3 mmol/L) (PP4_Moderate; PMID:17186219).
PP1_Strong	✔	This variant segregated with diabetes, with at least 7 informative meioses in 14 families with MODY (PP1_Strong; internal lab contributors).
PS3_Moderate	✔	A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Arg397Leu has RAI=0.72, which is less than or equal to the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID 17186219).

PS4		✔	This variant was identified in 21 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID:17186219 , 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 0.925 which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting		✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Curation History

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