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Variant: NM_000162.5(GCK):c.1322C>G (p.Ser441Trp)

Version: 1.0

CA367397017

1320655 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5a5a400f-b924-4261-a797-30b4d0f80434
Approved on: 2023/6/25
Published on: 2023/6/25

HGVS expressions

NM_000162.5(GCK):c.1322C>G (p.Ser441Trp)
NM_000162.5:c.1322C>G
NC_000007.14:g.44145212G>C
CM000669.2:g.44145212G>C
NC_000007.13:g.44184811G>C
CM000669.1:g.44184811G>C
NC_000007.12:g.44151336G>C
NG_008847.1:g.49212C>G
NG_008847.2:g.57959C>G
ENST00000395796.8:c.*1320C>G
ENST00000616242.5:c.*442C>G
ENST00000683378.1:n.548C>G
ENST00000336642.9:c.356C>G
ENST00000345378.7:c.1325C>G
ENST00000403799.8:c.1322C>G
ENST00000671824.1:c.1385C>G
ENST00000672743.1:n.334C>G
ENST00000673284.1:c.1322C>G
ENST00000336642.8:c.374C>G
ENST00000345378.6:c.1325C>G
ENST00000395796.7:c.1319C>G
ENST00000403799.7:c.1322C>G
ENST00000437084.1:c.1271C>G
ENST00000459642.1:n.702C>G
ENST00000616242.4:c.1319C>G
NM_000162.3:c.1322C>G
NM_033507.1:c.1325C>G
NM_033508.1:c.1319C>G
NM_000162.4:c.1322C>G
NM_001354800.1:c.1322C>G
NM_001354801.1:c.311C>G
NM_001354802.1:c.182C>G
NM_001354803.1:c.356C>G
NM_033507.2:c.1325C>G
NM_033508.2:c.1319C>G
NM_033507.3:c.1325C>G
NM_033508.3:c.1319C>G

NM_001354803.2:c.356C>G

Pathogenic

Met criteria codes 6

PP2 PP3 PM2_Supporting PP4_Moderate PS3_Moderate PS4

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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1322C>G variant in the glucokinase gene, GCK, causes an amino acid change of glycine to asparagine at codon 441 (p.(Ser441Trp)) 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 0.967, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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 OGTT increment < 3.0 mmol/L) (PP4_Moderate; PMID: 25665835). 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.Ser441Trp has RAI=0.11, which is less than the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID 19884385). This variant was identified in 8 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID: 27420379, 25665835, 19884385, 17573900, 16965331, 11508276, internal lab contributors). In summary, 1322C>G meets the criteria to be classified as likely 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, PP4_Moderate, PS3, PS4.

Met criteria codes

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.
PP3	✔	Variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.967, which is greater than the MDEP VCEP threshold of 0.70.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1.
PP4_Moderate	✔	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 OGTT increment < 3.0 mmol/L) (PP4_Moderate; PMID: 25665835)
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.Ser441Trp has RAI=0.11, which is less than or equal to the MDEP VCEP threshold of 0.50 (PS3_Moderate; PMID 19884385).

PS4		✔	This variant was identified in 8 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID: 27420379, 25665835, 19884385, 17573900, 16965331, 11508276, internal lab contributors).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000162.5(GCK):c.1322C>G (p.Ser4…	Pathogenic	Monogenic Diabetes	2023-06-25	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.0.0	GCK

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