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Variant: NM_033508.3:c.499A>G

Version: 1.0

CA367401753

2574157 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5c44fac3-f3a0-47a6-8ca6-7f4d29b17cc0
Approved on: 2023/7/28
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HGVS expressions

NM_033508.3:c.499A>G
NC_000007.14:g.44150046T>C
CM000669.2:g.44150046T>C
NC_000007.13:g.44189645T>C
CM000669.1:g.44189645T>C
NC_000007.12:g.44156170T>C
NG_008847.1:g.44378A>G
NG_008847.2:g.53125A>G
ENST00000395796.8:c.*500A>G
ENST00000616242.5:c.502A>G
ENST00000682635.1:n.988A>G
ENST00000345378.7:c.505A>G
ENST00000403799.8:c.502A>G
ENST00000671824.1:c.502A>G
ENST00000673284.1:c.502A>G
ENST00000345378.6:c.505A>G
ENST00000395796.7:c.499A>G
ENST00000403799.7:c.502A>G
ENST00000437084.1:c.451A>G
ENST00000616242.4:c.499A>G
NM_000162.3:c.502A>G
NM_033507.1:c.505A>G
NM_033508.1:c.499A>G
NM_000162.4:c.502A>G
NM_001354800.1:c.502A>G
NM_033507.2:c.505A>G
NM_033508.2:c.499A>G
NM_000162.5:c.502A>G
NM_033507.3:c.505A>G

Pathogenic

Met criteria codes 7

PM2_Supporting PP2 PP3 PM1 PS3_Moderate PS4_Moderate PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Evidence Links 0

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.502A>G variant in the glucokinase gene, GCK causes an amino acid change of Thr to Ala at codon 168 (p.(Thr168Ala)) 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 0.9739, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 4 unrelated individuals with diabetes (PS4_Moderate; PMID: 30592380, 23155716, 25015100, 18382660, 18571549, 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 negative antibodies/ OGTT glucose increment < 3 mmol/L) (PP4_Moderate; PMIDs: 30592380, 18382660). 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.Thr168Ala variant has RAI<0.50 (PS3_Moderate; PMID 18571549). This variant resides in an amino acid within the GCK glucose interaction domain that makes an H-bond interaction with glucose, which is defined as critical for the protein's function by the GlinGen MDEP (PM1). 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): PM2_Supporting, PP2, PM1, PP3, PS3_Moderate, PP4_Moderate, PS4_Moderate .

Met criteria codes

PM2_Supporting	✔	This variant is absent from 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 0.9739, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM1	✔	This variant resides in an amino acid within the GCK glucose interaction domain that makes an H-bond interaction with glucose, which is defined as critical for the protein's function by the GlinGen MDEP (PM1).
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 variant has RAI<0.50 (PS3_Moderate; PMID 18571549).
PS4_Moderate	✔	This variant was identified in 4 unrelated individuals with diabetes/hyperglycemia (PS4_Moderate; PMID: 30592380, 23155716, 25015100, 18382660, 18571549, internal lab contributors).
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 negative antibodies/ OGTT glucose increment < 3 mmol/L) (PP4_Moderate; PMIDs: 30592380, 18382660).

Curation History

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