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

Version: 1.0

CA367401755

2574158 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: c9164d1b-a076-4172-9de1-ae376621d484
Approved on: 2023/7/29
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HGVS expressions

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

Pathogenic

Met criteria codes 9

PS4_Moderate PP2 PP3 PM1 PM5_Strong PP4_Moderate PM2_Supporting PP1_Strong PS3_Supporting

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>C variant in the glucokinase gene, GCK causes an amino acid change of The to Pro at codon 168 (p.(Thr168Pro)) 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 0.988, 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; internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 3 generation family history of diabetes/hyperglycemia) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes with 5 informative meioses in 3 families with diabetes (PP1_Strong; PMID:9049484, internal lab contributors). This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, but the wild-type ATP Km is not between 0.4-0.65, and the p.Gly175Arg has Kcat/S0.5<0.5 (PS3_Supporting; PMID 10525657). The c.502A>G, p.Thr168Ala and c.503C>A, p.Thr168Asn variants have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong). 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 1.2.0, approved 6/7/2023): PM2_Supporting, PP2, PM1, PP3, PS3_Supporting, PP1_Strong, PM5_Strong, PS4_Moderate, PP4_Moderate.

Met criteria codes

PS4_Moderate	This variant was identified in 4 unrelated individuals with diabetes (PS4_Moderate; 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 0.988, 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).
PM5_Strong	The c.502A>G, p.Thr168Ala and c.503C>A, p.Thr168Asn variants have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong).
PP4_Moderate	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and 3 generation family history of diabetes/hyperglycemia) (PP4_Moderate; internal lab contributors).
PM2_Supporting	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

PP1_Strong		✔	This variant segregated with diabetes with 5 informative meioses in 3 families with hyperglycemia (PP1_Strong; PMID:9049484, internal lab contributors).
PS3_Supporting		✔	A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters passed the quality control, but the wild-type ATP Km is not between 0.4-0.65, and the p.Gly175Arg has Kcat/S0.5<0.5 (PS3_Supporting; PMID 10525657).

Curation History

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