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Variant: NM_000162.5(GCK):c.1148C>T (p.Ser383Leu)

Version: 1.0

CA10581499

236014 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 585d0bc1-7940-4c9b-aa3c-faf9a98a90a8
Approved on: 2024/2/28
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HGVS expressions

NM_000162.5:c.1148C>T
NM_000162.5(GCK):c.1148C>T (p.Ser383Leu)
NC_000007.14:g.44145602G>A
CM000669.2:g.44145602G>A
NC_000007.13:g.44185201G>A
CM000669.1:g.44185201G>A
NC_000007.12:g.44151726G>A
NG_008847.1:g.48822C>T
NG_008847.2:g.57569C>T
ENST00000395796.8:c.*1146C>T
ENST00000616242.5:c.*268C>T
ENST00000683378.1:n.374C>T
ENST00000336642.9:c.182C>T
ENST00000345378.7:c.1151C>T
ENST00000403799.8:c.1148C>T
ENST00000671824.1:c.1211C>T
ENST00000672743.1:n.160C>T
ENST00000673284.1:c.1148C>T
ENST00000336642.8:c.200C>T
ENST00000345378.6:c.1151C>T
ENST00000395796.7:c.1145C>T
ENST00000403799.7:c.1148C>T
ENST00000437084.1:c.1097C>T
ENST00000459642.1:n.528C>T
ENST00000616242.4:c.1145C>T
NM_000162.3:c.1148C>T
NM_033507.1:c.1151C>T
NM_033508.1:c.1145C>T
NM_000162.4:c.1148C>T
NM_001354800.1:c.1148C>T
NM_001354801.1:c.137C>T
NM_001354802.1:c.8C>T
NM_001354803.1:c.182C>T
NM_033507.2:c.1151C>T
NM_033508.2:c.1145C>T
NM_033507.3:c.1151C>T
NM_033508.3:c.1145C>T

NM_001354803.2:c.182C>T

Pathogenic

Met criteria codes 7

PP1_Strong | PS3_Moderate | PS4 | PM2_Supporting | PP2 | PP3 | PP4_Moderate

Not Met criteria codes 1

PM1

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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1148C>T variant in the glucokinase gene, GCK, causes an amino acid change of serine to leucine at codon 383 (p. (Ser383Leu)) 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 located in the larger hexokinase domain of the GCK gene (PMID: 31638168) but this variant does not reside in an amino acid that directly binds glucose or ATP, which is defined as critical for the protein's function by the ClinGen MDEP, so it does not meet PM1. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.831 which is greater than the MDEP VCEP threshold of 0.70 (PP3). MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.20, which is below the MDEP cutoff (<0.5) (Matschinsky FM, Magnuson MA (eds): Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics. Front. Diabetes. Basel, Karger, 2004, vol 16, pp 92–109). This variant has been identified in at least 53 unrelated individuals with hyperglycemia and segregated with the phenotype, with 30 informative meioses in 49 families (PS4, PP1_Strong; PMID: 28555465, 30663027, 34462253, 34746319, internal lab contributors). At least of of these patients had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%, negative GAD-65 (PP4_Moderate; PMID: 28555465). In summary, c.1148C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (VCEP specifications version v1.3.0; approved 8/11/2023): PP3, PS4, PP4_Moderate, PP2, PP1_Strong, PM2_Supporting

Met criteria codes

PP1_Strong	✔	PP1_strong This variant segregated with hyperglycemia, with 30 informative meioses in 49 families (PP1_Strong; PMID: 28555465, internal lab contributors).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.20, which is below the MDEP cutoff (<0.5) (Matschinsky FM, Magnuson MA (eds): Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics. Front. Diabetes. Basel, Karger, 2004, vol 16, pp 92–109).
PS4	✔	This variant was identified in at least 53 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 28555465, 30663027, 34462253, 34746319, Internal lab contributors).
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		✔	REVEL 0.831
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%, negative GAD-65 (PP4_Moderate; PMID: 28555465).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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