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Variant: NM_001354803.2:c.181T>A

Version: 1.0

CA367398738

3024419 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: a26d1bf6-3832-4b9b-a24f-7297c71da089
Approved on: 2024/2/28
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HGVS expressions

NM_001354803.2:c.181T>A
NC_000007.14:g.44145603A>T
CM000669.2:g.44145603A>T
NC_000007.13:g.44185202A>T
CM000669.1:g.44185202A>T
NC_000007.12:g.44151727A>T
NG_008847.1:g.48821T>A
NG_008847.2:g.57568T>A
ENST00000395796.8:c.*1145T>A
ENST00000616242.5:c.*267T>A
ENST00000683378.1:n.373T>A
ENST00000336642.9:c.181T>A
ENST00000345378.7:c.1150T>A
ENST00000403799.8:c.1147T>A
ENST00000671824.1:c.1210T>A
ENST00000672743.1:n.159T>A
ENST00000673284.1:c.1147T>A
ENST00000336642.8:c.199T>A
ENST00000345378.6:c.1150T>A
ENST00000395796.7:c.1144T>A
ENST00000403799.7:c.1147T>A
ENST00000437084.1:c.1096T>A
ENST00000459642.1:n.527T>A
ENST00000616242.4:c.1144T>A
NM_000162.3:c.1147T>A
NM_033507.1:c.1150T>A
NM_033508.1:c.1144T>A
NM_000162.4:c.1147T>A
NM_001354800.1:c.1147T>A
NM_001354801.1:c.136T>A
NM_001354802.1:c.7T>A
NM_001354803.1:c.181T>A
NM_033507.2:c.1150T>A
NM_033508.2:c.1144T>A
NM_000162.5:c.1147T>A
NM_033507.3:c.1150T>A
NM_033508.3:c.1144T>A

Likely Pathogenic

Met criteria codes 6

PP2 PP3 PM2 PP4_Moderate PM5_Supporting PS4_Moderate

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.1147T>A variant in the glucokinase gene, GCK, causes an amino acid change of serine to threonine at codon 383 (p. (Ser383Thr)) 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 0.73 which is greater than the MDEP VCEP threshold of 0.70 (PP3). Another missense variant, c.1148C>T (p.Ser383Leu), has been interpreted as pathogenic by the ClinGen MDEP, but has a greater Grantham distance than p.Ser383Thr (PM5_Supporting). This variant was identified in 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 28726111, internal lab contributors). One of these individuals has a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID:28726111). In summary, c.1147T>A meets the criteria to be classified as likely 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, PP2, PM5_Supporting, PM2_Supporting, PP4_Moderate, PS4_Moderate

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 (PP2).
PP3	✔	REVEL 0.73
PM2	✔	Absent from gnomAD v2.1.
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 negative antibodies) (PP4_Moderate; PMID:28726111).
PM5_Supporting	✔	Another missense variant, c.1148C>T (p.Ser383Leu), has been interpreted as pathogenic by the ClinGen MDEP, but has a greater Grantham distance than p.Ser383Thr (PM5_Supporting).
PS4_Moderate	✔	

This variant was identified in 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 28726111, internal lab contributors).

Curation History

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