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Variant: NM_000162.5(GCK):c.1142T>G (p.Met381Arg)

Version: 1.0

CA213719

36178 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 54862117-14b2-4c5d-8e05-9ac0d6c61ee2
Approved on: 2023/7/17
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HGVS expressions

NM_000162.5(GCK):c.1142T>G (p.Met381Arg)
NM_000162.5:c.1142T>G
NC_000007.14:g.44145608A>C
CM000669.2:g.44145608A>C
NC_000007.13:g.44185207A>C
CM000669.1:g.44185207A>C
NC_000007.12:g.44151732A>C
NG_008847.1:g.48816T>G
NG_008847.2:g.57563T>G
ENST00000395796.8:c.*1140T>G
ENST00000616242.5:c.*262T>G
ENST00000683378.1:n.368T>G
ENST00000336642.9:c.176T>G
ENST00000345378.7:c.1145T>G
ENST00000403799.8:c.1142T>G
ENST00000671824.1:c.1205T>G
ENST00000672743.1:n.154T>G
ENST00000673284.1:c.1142T>G
ENST00000336642.8:c.194T>G
ENST00000345378.6:c.1145T>G
ENST00000395796.7:c.1139T>G
ENST00000403799.7:c.1142T>G
ENST00000437084.1:c.1091T>G
ENST00000459642.1:n.522T>G
ENST00000616242.4:c.1139T>G
NM_000162.3:c.1142T>G
NM_033507.1:c.1145T>G
NM_033508.1:c.1139T>G
NM_000162.4:c.1142T>G
NM_001354800.1:c.1142T>G
NM_001354801.1:c.131T>G
NM_001354802.1:c.2T>G
NM_001354803.1:c.176T>G
NM_033507.2:c.1145T>G
NM_033508.2:c.1139T>G
NM_033507.3:c.1145T>G
NM_033508.3:c.1139T>G

NM_001354803.2:c.176T>G

Likely Pathogenic

Met criteria codes 6

PM5 PS4_Moderate PM2_Supporting PP2 PP3 PP4_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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1142T>G variant in the glucokinase gene, GCK, causes an amino acid change of methionine to arginine at codon 381 (p.(Met381Arg)) 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 predicted to be deleterious by computational evidence, with a REVEL score of 0.9629, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting), and was identified in 5 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID 22060211 (likely same cases as PMID 29927023, PMID 32375122, PMID 2555642, and PMID 24804978 (Kawakita et al 2014)), PMID 24804978, internal lab contributors). At least one of these individuals has a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). Another missense variant, c.1142T>C (p.Met381Thr, has been interpreted as pathogenic by the ClinGen MDEP, and p.Met381Arg has a greater Grantham distance (PM5). In summary, the c.1142T>G variant 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): PP4_Moderate, PM5, PS4_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PM5	✔	Another missense variant, c.1142T>C (p.Met381Thr, has been interpreted as pathogenic by the ClinGen MDEP, and p.Met381Arg has a greater Grantham distance (PM5). (GD for p.Met381Thr = 81, GD for p.Met381Arg = 101).
PS4_Moderate	✔	This variant was identified in 5 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID 22060211 (likely same cases as PMID 29927023, PMID 32375122, PMID 2555642, and PMID 24804978 (Kawakita et al 2014)), PMID 24804978, 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	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.9629, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

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 negative antibodies) (PP4_Moderate; internal lab contributors).

Curation History

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