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Variant: NM_000162.5(GCK):c.1310C>T (p.Thr437Ile)

Version: 1.0

CA367397075

585914 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 4b83ef1c-7966-4743-bfa2-d35cf794ab74
Approved on: 2024/1/28
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HGVS expressions

NM_000162.5(GCK):c.1310C>T (p.Thr437Ile)
NM_000162.5:c.1310C>T
NC_000007.14:g.44145224G>A
CM000669.2:g.44145224G>A
NC_000007.13:g.44184823G>A
CM000669.1:g.44184823G>A
NC_000007.12:g.44151348G>A
NG_008847.1:g.49200C>T
NG_008847.2:g.57947C>T
ENST00000395796.8:c.*1308C>T
ENST00000616242.5:c.*430C>T
ENST00000683378.1:n.536C>T
ENST00000336642.9:c.344C>T
ENST00000345378.7:c.1313C>T
ENST00000403799.8:c.1310C>T
ENST00000671824.1:c.1373C>T
ENST00000672743.1:n.322C>T
ENST00000673284.1:c.1310C>T
ENST00000336642.8:c.362C>T
ENST00000345378.6:c.1313C>T
ENST00000395796.7:c.1307C>T
ENST00000403799.7:c.1310C>T
ENST00000437084.1:c.1259C>T
ENST00000459642.1:n.690C>T
ENST00000616242.4:c.1307C>T
NM_000162.3:c.1310C>T
NM_033507.1:c.1313C>T
NM_033508.1:c.1307C>T
NM_000162.4:c.1310C>T
NM_001354800.1:c.1310C>T
NM_001354801.1:c.299C>T
NM_001354802.1:c.170C>T
NM_001354803.1:c.344C>T
NM_033507.2:c.1313C>T
NM_033508.2:c.1307C>T
NM_033507.3:c.1313C>T
NM_033508.3:c.1307C>T

NM_001354803.2:c.344C>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting | PP2 | PP3 | PS4_Moderate | 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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1310C>T variant in the glucokinase gene, GCK, causes an amino acid change of threonine to isoleucine at codon 437 (p.(Thr437Ile)) 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 0.7269, 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 4 unrelated individuals with hyperglycemia; (PS4_Moderate; ClinVar ID 585914, PMID 28323911, internal lab contributors). Two of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and documented persistent impaired fasting glucose or negative antibodies) (PP4_Moderate; PMID: 28323911, internal lab contributors). In summary, c.1310C>T meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PS4_Moderate, PP2, PP3, PM2_Supporting, PP4_Moderate.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). v4.0: Meets Grpmax FAF (0.000001320 < 000003) but 5 copies in ENF
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 0.7269, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4_Moderate	✔	This variant was identified in 4 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; (PS4_Moderate; ClinVar ID 585914, PMID 28323911, internal lab contributors).
PP4_Moderate	✔	This variant was identified in 2 individuasl with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and documented persistent impaired fasting glucose or negative antibodies) (PP4_Moderate; PMID: 28323911, internal lab contributors).

Curation History

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