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Variant: NM_000162.5(GCK):c.1307T>A (p.Ile436Asn)

Version: 1.0

CA213751

36195 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 848bb6b5-a99b-41c3-a9b8-413c2dce18db
Approved on: 2024/4/27
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HGVS expressions

NM_000162.5:c.1307T>A
NM_000162.5(GCK):c.1307T>A (p.Ile436Asn)
NC_000007.14:g.44145227A>T
CM000669.2:g.44145227A>T
NC_000007.13:g.44184826A>T
CM000669.1:g.44184826A>T
NC_000007.12:g.44151351A>T
NG_008847.1:g.49197T>A
NG_008847.2:g.57944T>A
ENST00000395796.8:c.*1305T>A
ENST00000616242.5:c.*427T>A
ENST00000683378.1:n.533T>A
ENST00000336642.9:c.341T>A
ENST00000345378.7:c.1310T>A
ENST00000403799.8:c.1307T>A
ENST00000671824.1:c.1370T>A
ENST00000672743.1:n.319T>A
ENST00000673284.1:c.1307T>A
ENST00000336642.8:c.359T>A
ENST00000345378.6:c.1310T>A
ENST00000395796.7:c.1304T>A
ENST00000403799.7:c.1307T>A
ENST00000437084.1:c.1256T>A
ENST00000459642.1:n.687T>A
ENST00000616242.4:c.1304T>A
NM_000162.3:c.1307T>A
NM_033507.1:c.1310T>A
NM_033508.1:c.1304T>A
NM_000162.4:c.1307T>A
NM_001354800.1:c.1307T>A
NM_001354801.1:c.296T>A
NM_001354802.1:c.167T>A
NM_001354803.1:c.341T>A
NM_033507.2:c.1310T>A
NM_033508.2:c.1304T>A
NM_033507.3:c.1310T>A
NM_033508.3:c.1304T>A

NM_001354803.2:c.341T>A

Pathogenic

Met criteria codes 8

PP2 PP3 PP1_Strong PP4_Moderate PS3_Supporting PM2_Supporting 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.1307T>A variant in the glucokinase gene, GCK, causes an amino acid change of isoleucine to asparagine at codon 436 (p.(Ile436Asn)) 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 0.957, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in at least 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMID 17204055, PMID 20337973, PMID 22493702, internal lab contributors). At least 2 of these individuals have a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies +/- 2 hour oral glucose tolerance test increment <3 mmol/L) (PP4_Moderate; internal lab contributors). This variant also segregated with diabetes/hyperglycemia, with 4 informative meioses in 2 families (PP1_Strong; internal lab contributors). Another missense variant, c.1306A>T p.Ile436Phe has been interpreted as likely pathogenic by the ClinGen MDEP (PM5_Supporting). While the RAI of this variant was 0.975, this variant results in decreased inhibition by GKRP (PS3_Supporting; PMID: 22493702). In summary, this evidence supports the classification of c.1307T>A as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_Strong, PS4_Moderate, PP4_Moderate, PM5_Supporting, PP2, PP3, PM2_Supporting.

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	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.957, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia, with 4 informative meioses in 2 families (PP1_Strong; internal lab contributors).
PP4_Moderate	✔	This variant was identified in 2 unrelated individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies +/- 2 hour oral glucose tolerance test increment <3 mmol/L).

PS3_Supporting	✔	While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, and a relative stability index (RSI) was not calculated, the variant did exhibit marked thermal instability as well as decreased inhibition by GKRP (PS3_Supporting).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.1306A>T p.Ile436Phe has been interpreted as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
PS4_Moderate	✔	This variant was identified in at least 5 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID 17204055, PMID 20337973, PMID 22493702, internal lab contributors).

Curation History

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