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Variant: NM_000162.5(GCK):c.442T>A (p.Phe148Ile)

Version: 1.0

CA367401967

447399 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 8ed90963-6a32-49a2-b4fd-3598a2ac3df0
Approved on: 2023/10/2
Published on: 2023/10/2

HGVS expressions

NM_000162.5(GCK):c.442T>A (p.Phe148Ile)
NM_000162.5:c.442T>A
NC_000007.14:g.44150997A>T
CM000669.2:g.44150997A>T
NC_000007.13:g.44190596A>T
CM000669.1:g.44190596A>T
NC_000007.12:g.44157121A>T
NG_008847.1:g.43427T>A
NG_008847.2:g.52174T>A
ENST00000395796.8:c.*440T>A
ENST00000616242.5:c.442T>A
ENST00000682635.1:n.928T>A
ENST00000345378.7:c.445T>A
ENST00000403799.8:c.442T>A
ENST00000671824.1:c.442T>A
ENST00000673284.1:c.442T>A
ENST00000345378.6:c.445T>A
ENST00000395796.7:c.439T>A
ENST00000403799.7:c.442T>A
ENST00000437084.1:c.391T>A
ENST00000616242.4:c.439T>A
NM_000162.3:c.442T>A
NM_033507.1:c.445T>A
NM_033508.1:c.439T>A
NM_000162.4:c.442T>A
NM_001354800.1:c.442T>A
NM_033507.2:c.445T>A
NM_033508.2:c.439T>A
NM_033507.3:c.445T>A
NM_033508.3:c.439T>A

Uncertain Significance

Met criteria codes 4

PP2 PP3 PP4 PM2_Supporting

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.442T>A variant in the glucokinase gene, GCK, causes an amino acid change of phenylalanine to isoleucine at codon 148 (p.(Phe148Ile)) 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 predicted to be deleterious by computational evidence, with a REVEL score of 0.986, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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%) (PP4; internal lab contributor). In summary, c.442T>A meets the criteria to be classified as a variant of uncertain significance for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM2_Supporting, PP2, PP3, PP4.

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 0.986, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4	✔	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%) (PP4; internal lab contributor).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000162.5(GCK):c.442T>A (p.Phe14...	Uncertain Significance	Monogenic Diabetes	2023-10-02	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0	GCK

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