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Variant: NM_000162.5(GCK):c.566T>C (p.Ile189Thr)

Version: 1.0

CA367401550

431972 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7e0e63cf-14f1-40ba-9af0-8f9179fc282a
Approved on: 2023/5/8
Published on: 2023/5/8

HGVS expressions

NM_000162.5:c.566T>C
NM_000162.5(GCK):c.566T>C (p.Ile189Thr)
NC_000007.14:g.44149982A>G
CM000669.2:g.44149982A>G
NC_000007.13:g.44189581A>G
CM000669.1:g.44189581A>G
NC_000007.12:g.44156106A>G
NG_008847.1:g.44442T>C
NG_008847.2:g.53189T>C
ENST00000395796.8:c.*564T>C
ENST00000616242.5:c.566T>C
ENST00000682635.1:n.1052T>C
ENST00000345378.7:c.569T>C
ENST00000403799.8:c.566T>C
ENST00000671824.1:c.566T>C
ENST00000673284.1:c.566T>C
ENST00000345378.6:c.569T>C
ENST00000395796.7:c.563T>C
ENST00000403799.7:c.566T>C
ENST00000437084.1:c.515T>C
ENST00000616242.4:c.563T>C
NM_000162.3:c.566T>C
NM_033507.1:c.569T>C
NM_033508.1:c.563T>C
NM_000162.4:c.566T>C
NM_001354800.1:c.566T>C
NM_033507.2:c.569T>C
NM_033508.2:c.563T>C
NM_033507.3:c.569T>C
NM_033508.3:c.563T>C

Pathogenic

Met criteria codes 6

PP1_Strong | PM2_Supporting | PS4 | PP2 | PP3 | PP4

Not Met criteria codes 1

PM1

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 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.566T>C variant in the glucokinase gene, GCK, causes an amino acid change of isoleucine to threonine at codon 189 (p.Ile189Thr) of NM_000162.5. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.969, which is greater than the MDEP VCEP threshold of 0.70 (PP3) and 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 was identified in 7 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; internal lab contributors). Additionally, this variant was identified in at least one individual with a clinical history highly specific for GCK-MODY (fasting glucose = 125 mg/dl and HbA1c = 6.5%) (PP4, internal lab contributors). Lastly, this variant segregated with diabetes, with five informative meioses in two families with MODY (PP1_Strong; internal lab contributors). In summary, c.566T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.1.0, approved 3/23/2023): PM2_Supporting, PP3, PP2, PP4, PP1_Strong, PS4.

Met criteria codes

PP1_Strong	✔	5 meioses in 2 families (internal lab contributors)
PM2_Supporting	✔	Absent from gnomAD
PS4	✔	7 unrelated cases from internal lab contributors
PP2	✔	Missense variant in GCK
PP3	✔	REVEL = 0.969
PP4	✔	Identified in a patient with fasting glucose of 125 mg/dl and HbA1c = 6.5% (internal laboratory collaborators).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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