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Variant: NM_000162.5(GCK):c.1124C>T (p.Ser375Phe)

Version: 1.0

CA213713

36175 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7e5614a3-39a9-4c90-83ce-bb5af3514d80
Approved on: 2024/12/2
Published on: 2024/12/2

HGVS expressions

NM_000162.5:c.1124C>T
NM_000162.5(GCK):c.1124C>T (p.Ser375Phe)
NC_000007.14:g.44145626G>A
CM000669.2:g.44145626G>A
NC_000007.13:g.44185225G>A
CM000669.1:g.44185225G>A
NC_000007.12:g.44151750G>A
NG_008847.1:g.48798C>T
NG_008847.2:g.57545C>T
ENST00000395796.8:c.*1122C>T
ENST00000616242.5:c.*244C>T
ENST00000683378.1:n.350C>T
ENST00000336642.9:c.158C>T
ENST00000345378.7:c.1127C>T
ENST00000403799.8:c.1124C>T
ENST00000671824.1:c.1187C>T
ENST00000672743.1:n.136C>T
ENST00000673284.1:c.1124C>T
ENST00000336642.8:c.176C>T
ENST00000345378.6:c.1127C>T
ENST00000395796.7:c.1121C>T
ENST00000403799.7:c.1124C>T
ENST00000437084.1:c.1073C>T
ENST00000459642.1:n.504C>T
ENST00000616242.4:c.1121C>T
NM_000162.3:c.1124C>T
NM_033507.1:c.1127C>T
NM_033508.1:c.1121C>T
NM_000162.4:c.1124C>T
NM_001354800.1:c.1124C>T
NM_001354801.1:c.113C>T
NM_001354802.1:c.-17C>T
NM_001354803.1:c.158C>T
NM_033507.2:c.1127C>T
NM_033508.2:c.1121C>T
NM_033507.3:c.1127C>T
NM_033508.3:c.1121C>T

NM_001354803.2:c.158C>T

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PP2 PP3 PM2_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.1124C>T variant in the glucokinase gene, GCK, causes an amino acid change of serine to phenylalanine at codon 375 (p.(Ser375Phe)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). 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). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 4 unrelated individuals with hyperglycemia (PS4; ClinVar 36175, internal lab contributors). The variant was identified in an individual with a clinical history highly specific for GCK-MODY (fasting glucose 5.5-8 mol/L and HbA1c 5.6-7.6% and three-generation, dominant family history of hyperglycemia. (PP4_Moderate; internal lab contributors). In summary, this variant meets the criteria to be classified as likely pathogenic for GCK-MODY. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2.0, approved 6/7/2023): PP2, PP3, PM2_Supporting, PP4_Moderate, PS4_Moderate.

Met criteria codes

PP4_Moderate	✔	The variant was identified in an individual with a clinical history highly specific for GCK-MODY (fasting glucose 5.5-8 mol/L and HbA1c 5.6-7.6% and three-generation, dominant family history of hyperglycemia) (PP4_Moderate; internal lab contributors).
PP2	✔	GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.969, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in 4 unrelated individuals with hyperglycemia (PS4; ClinVar, internal lab contributors).

Curation History

Showing 1 to 1 of 1 rows

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