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Variant: NM_000162.5(GCK):c.449T>C (p.Phe150Ser)

Version: 1.0

CA213784

36218 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 2f1f3c66-5829-44e1-a27b-080c80bfdb5f
Approved on: 2024/3/22
Published on: 2024/3/22

HGVS expressions

NM_000162.5:c.449T>C
NM_000162.5(GCK):c.449T>C (p.Phe150Ser)
NC_000007.14:g.44150990A>G
CM000669.2:g.44150990A>G
NC_000007.13:g.44190589A>G
CM000669.1:g.44190589A>G
NC_000007.12:g.44157114A>G
NG_008847.1:g.43434T>C
NG_008847.2:g.52181T>C
ENST00000395796.8:c.*447T>C
ENST00000616242.5:c.449T>C
ENST00000682635.1:n.935T>C
ENST00000345378.7:c.452T>C
ENST00000403799.8:c.449T>C
ENST00000671824.1:c.449T>C
ENST00000673284.1:c.449T>C
ENST00000345378.6:c.452T>C
ENST00000395796.7:c.446T>C
ENST00000403799.7:c.449T>C
ENST00000437084.1:c.398T>C
ENST00000616242.4:c.446T>C
NM_000162.3:c.449T>C
NM_033507.1:c.452T>C
NM_033508.1:c.446T>C
NM_000162.4:c.449T>C
NM_001354800.1:c.449T>C
NM_033507.2:c.452T>C
NM_033508.2:c.446T>C
NM_033507.3:c.452T>C
NM_033508.3:c.446T>C

Pathogenic

Met criteria codes 6

PP2 PP3 PM5 PP1_Strong PS4 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.449T>C variant in the glucokinase gene, GCK, causes an amino acid change of phenylalanine to serine at codon 150 (p.(Phe150Ser)) 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 predicted to be deleterious by computational evidence, with a REVEL score of 0.983, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has a gnomAD v4.0.0 Popmax filtering allele frequency of 0 (below the MDEP threshold of 0.000003), and ≤ 2 copies observed in the European non-Finnish population and any other subpopulation, thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting). This variant was identified in at least 28 unrelated individuals with hyperglycemia (PS4; PMIDs: 15305805, 30191644, internal lab contributors). This variant segregated with hyperglycemia, with at least 19 informative meioses in multiple families (PP1_Strong; internal lab contributors). Another missense variant, c.449T>A p.Phe150Tyr has been interpreted as pathogenic by the ClinGen MDEP, and p.Phe150Ser has a greater Grantham distance (PM5). In summary, c.449T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0 approved 8/11/2023): PS4, PP1_Strong, PM2_Supporting, PP3, PP2, PM5.

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 0.983, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5	✔	Another missense variant, c.449T>A p.Phe150Tyr has been interpreted as pathogenic by the ClinGen MDEP, and p.Phe150Ser has a greater Grantham distance (PM5).
PP1_Strong	✔	This variant segregated with hyperglycemia, with at least 19 informative meioses in multiple families (PP1_Strong; internal lab contributors).
PS4	✔	This variant was identified in at least 28 unrelated individuals with hyperglycemia (PS4; PMIDs: 15305805, 30191644, internal lab contributors).
PM2_Supporting	✔	This variant has a gnomAD v4.0.0 Popmax filtering allele frequency of 0 (below the MDEP threshold of 0.000003), and ≤ 2 copies observed in the European non-Finnish population and any other subpopulation, thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting).

Curation History

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