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Variant: NM_000162.5(GCK):c.601G>T (p.Ala201Ser)

Version: 1.0

CA246541

198050 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e88a1f47-bc1b-4f78-bda7-6d240f568d62
Approved on: 2024/2/23
Published on: 2024/2/23

HGVS expressions

NM_000162.5:c.601G>T
NM_000162.5(GCK):c.601G>T (p.Ala201Ser)
NC_000007.14:g.44149838C>A
CM000669.2:g.44149838C>A
NC_000007.13:g.44189437C>A
CM000669.1:g.44189437C>A
NC_000007.12:g.44155962C>A
NG_008847.1:g.44586G>T
NG_008847.2:g.53333G>T
ENST00000395796.8:c.*599G>T
ENST00000616242.5:c.601G>T
ENST00000682635.1:n.1087G>T
ENST00000345378.7:c.604G>T
ENST00000403799.8:c.601G>T
ENST00000671824.1:c.601G>T
ENST00000673284.1:c.601G>T
ENST00000345378.6:c.604G>T
ENST00000395796.7:c.598G>T
ENST00000403799.7:c.601G>T
ENST00000437084.1:c.550G>T
ENST00000616242.4:c.598G>T
NM_000162.3:c.601G>T
NM_033507.1:c.604G>T
NM_033508.1:c.598G>T
NM_000162.4:c.601G>T
NM_001354800.1:c.601G>T
NM_033507.2:c.604G>T
NM_033508.2:c.598G>T
NM_033507.3:c.604G>T
NM_033508.3:c.598G>T

Pathogenic

Met criteria codes 5

PP1_Strong | PP2 | PS4_Moderate | PM2_Supporting | PP4_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.601G>T variant in the glucokinase gene, GCK, causes an amino acid change of alanine to serine at codon 201 (p.(Ala201Ser)) 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 0.929, 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 four unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors). 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% and antibody negative) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes/hyperglycemia, with seven informative meioses in one family (PP1_Strong; internal lab contributors). In summary, c.605T>G 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): PM2_Supporting, PP2, PP3, PS4_Moderate, PP1_Strong, PP4_Moderate.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia, with seven informative meioses in one family (PP1_Strong; internal lab contributors).
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).
PS4_Moderate	✔	This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate	✔	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% and antibody negative) (PP4_Moderate; internal lab contributors).

Curation History

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