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Variant: NM_000162.5(GCK):c.898G>C (p.Glu300Gln)

Version: 2.0

CA367400083

2578349 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: dce33bbd-74df-4235-9cc1-e2ef0a02eeb9
Approved on: 2024/10/13
Published on: 2024/10/13

HGVS expressions

NM_000162.5(GCK):c.898G>C (p.Glu300Gln)
NM_000162.5:c.898G>C
NC_000007.14:g.44146584C>G
CM000669.2:g.44146584C>G
NC_000007.13:g.44186183C>G
CM000669.1:g.44186183C>G
NC_000007.12:g.44152708C>G
NG_008847.1:g.47840G>C
NG_008847.2:g.56587G>C
ENST00000395796.8:c.*896G>C
ENST00000616242.5:c.*18G>C
ENST00000683378.1:n.124G>C
ENST00000345378.7:c.901G>C
ENST00000403799.8:c.898G>C
ENST00000671824.1:c.961G>C
ENST00000673284.1:c.898G>C
ENST00000345378.6:c.901G>C
ENST00000395796.7:c.895G>C
ENST00000403799.7:c.898G>C
ENST00000437084.1:c.847G>C
ENST00000473353.1:n.196G>C
ENST00000616242.4:c.895G>C
NM_000162.3:c.898G>C
NM_033507.1:c.901G>C
NM_033508.1:c.895G>C
NM_000162.4:c.898G>C
NM_001354800.1:c.898G>C
NM_001354801.1:c.8+35G>C
NM_033507.2:c.901G>C
NM_033508.2:c.895G>C
NM_033507.3:c.901G>C
NM_033508.3:c.895G>C

Pathogenic

Met criteria codes 7

PP4_Moderate | PP1_Strong | PM2_Supporting | PM5_Supporting | PS4 | PP2 | PP3

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.898G>C variant in the glucokinase gene, GCK, causes an amino acid change of glutamic acid to glutamine at codon 300 (p.(Glu300Gln)) 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 0.964, 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 segregated with diabetes/fasting hyperglycemia with more than 20 informative meioses in multiple families (PP1_Strong; PMID: 8433729, internal lab contributors). This variant was identified in 8 unrelated individuals with hyperglycemia (PS4; PMID: 8433729, internal lab contributors). Additionally, one of these individuals was reported to have a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). Another missense variant, c.898G>A (p.Glu300Lys), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PP2, PP3, PM2_Supporting, PP1_Strong, PS4, PP4_Moderate, PM5_Supporting.

Met criteria codes

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 negative antibodies) (PP4_Moderate; internal lab contributors).
PP1_Strong	✔	This variant segregated with diabetes/fasting hyperglycemia with more than 20 informative meioses in multiple families (PP1_Strong; PMID: 8433729, internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.898G>A (p.Glu300Lys), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
PS4	✔	This variant was identified in 8 unrelated individuals with hyperglycemia (PS4; PMID: 8433729, 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).

PP3		✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.964, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Curation History

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