The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000162.5(GCK):c.883G>A (p.Gly295Ser)

Version: 1.0

CA367400140

447423 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: ec828f15-21d6-4ba9-bff0-580bd7e83688
Approved on: 2023/8/11
Published on: 2023/8/11

HGVS expressions

NM_000162.5:c.883G>A
NM_000162.5(GCK):c.883G>A (p.Gly295Ser)
NC_000007.14:g.44146599C>T
CM000669.2:g.44146599C>T
NC_000007.13:g.44186198C>T
CM000669.1:g.44186198C>T
NC_000007.12:g.44152723C>T
NG_008847.1:g.47825G>A
NG_008847.2:g.56572G>A
ENST00000395796.8:c.*881G>A
ENST00000616242.5:c.*3G>A
ENST00000683378.1:n.109G>A
ENST00000345378.7:c.886G>A
ENST00000403799.8:c.883G>A
ENST00000671824.1:c.946G>A
ENST00000673284.1:c.883G>A
ENST00000345378.6:c.886G>A
ENST00000395796.7:c.880G>A
ENST00000403799.7:c.883G>A
ENST00000437084.1:c.832G>A
ENST00000473353.1:n.181G>A
ENST00000616242.4:c.880G>A
NM_000162.3:c.883G>A
NM_033507.1:c.886G>A
NM_033508.1:c.880G>A
NM_000162.4:c.883G>A
NM_001354800.1:c.883G>A
NM_001354801.1:c.8+20G>A
NM_033507.2:c.886G>A
NM_033508.2:c.880G>A
NM_033507.3:c.886G>A
NM_033508.3:c.880G>A

Likely Pathogenic

Met criteria codes 6

PP4_Moderate | PM2_Supporting | PS4_Moderate | PM1 | 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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.883G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to serine at codon 295 (p.(Gly295Ser)) of NM_000162.5. This variant was identified in four unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID: 29510678 and internal lab contributors). At least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L) (PP4_Moderate; internal lab contributors). Additionally, this variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.956, which is greater than the MDEP VCEP threshold of 0.70 (PP3) and this variant 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). Lastly, this variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). In summary, c.883G>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PS4_Moderate, PP4_Moderate, PM2_Suporting, PP2, PP3, PM1.

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 OGTT increment < 3 mmol/L) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in four unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PMID: 29510678, internal lab contributors).
PM1	✔	This variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
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 0.956, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Curation History

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