

Variant: *NM_000162.5(GCK):c.898G>A (p.Glu300Lys)*

Version: 1.1

CA367400084 [↗](#)

1436793 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

UUID: 438267c6-7ce7-4fce-9f42-f771f15c6548

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HGVS expressions

NM_000162.5(GCK):c.898G>A (p.Glu300Lys)

NM_000162.5:c.898G>A

NC_000007.14:g.44146584C>T

CM000669.2:g.44146584C>T

NC_000007.13:g.44186183C>T

CM000669.1:g.44186183C>T

NC_000007.12:g.44152708C>T

NG_008847.1:g.47840G>A

NG_008847.2:g.56587G>A

ENST00000395796.8:c.*896G>A

ENST00000616242.5:c.*18G>A

ENST00000683378.1:n.124G>A

ENST00000345378.7:c.901G>A

ENST00000403799.8:c.898G>A

ENST00000671824.1:c.961G>A

ENST00000673284.1:c.898G>A

ENST00000345378.6:c.901G>A

ENST00000395796.7:c.895G>A

ENST00000403799.7:c.898G>A

ENST00000437084.1:c.847G>A

ENST00000473353.1:n.196G>A

ENST00000616242.4:c.895G>A

NM_000162.3:c.898G>A

NM_033507.1:c.901G>A

NM_033508.1:c.895G>A

NM_000162.4:c.898G>A

NM_001354800.1:c.898G>A

NM_001354801.1:c.8+35G>A

NM_033507.2:c.901G>A

NM_033508.2:c.895G>A

NM_033507.3:c.901G>A

NM_033508.3:c.895G>A

Likely Pathogenic

Met criteria codes 6

PP4_ModeratePP2PP3PM5PS3_SupportingPM2_Supporting

Not Met criteria codes 1

PS4

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>A variant in the glucokinase gene, GCK, causes an amino acid change of glutamic acid to lysine at codon 300 (p.(Glu300Lys)) 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 0.977, 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 three unrelated individuals with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold (PMIDs: 8433729, 22035297, 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 negative antibodies) (PP4_Moderate; internal lab contributors). Another missense variant, c.898G>C p.(Glu300Gln), has been classified as pathogenic by the ClinGen MDEP VCEP and has a lower Grantham distance than p.(Glu300Lys) (PM5). While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the variant was shown through a cellular assay to be unstable (PS3_Supporting; PMIDs: 10455021, 10525657, https://doi.org/10.1159/000079009). In summary, this variant meets the criteria to be classified as likely 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, PP4_Moderate, PM5, PS3_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).
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 0.977, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5		Another missense variant, c.898G>C p.(Glu300Gln), has been classified as pathogenic by the ClinGen MDEP VCEP and has a lower Grantham distance than p.(Glu300Lys) (PM5).
PS3_Supporting		While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the variant was shown through a cellular assay to be unstable (PS3_Supporting; PMIDs: 10455021, 10525657, https://doi.org/10.1159/000079009).
PM2_Supporting		This variant is absent from gnomAD v2.1.1 (PM2_Supporting).



Not Met criteria codes

PS4



This variant was identified in three unrelated individuals with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold (PMIDs: 8433729, 22035297, internal lab contributors).

Curation History

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