

Variant: *NM_000162.5(GCK):c.682A>G (p.Thr228Ala)*

Version: 1.0

CA367400790 [↗](#)

447413 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 58958324-9a8b-470d-aece-e0dc19575634

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HGVS expressions

NM_000162.5:c.682A>G

NM_000162.5(GCK):c.682A>G (p.Thr228Ala)

NC_000007.14:g.44147831T>C

CM000669.2:g.44147831T>C

NC_000007.13:g.44187430T>C

CM000669.1:g.44187430T>C

NC_000007.12:g.44153955T>C

NG_008847.1:g.46593A>G

NG_008847.2:g.55340A>G

ENST00000395796.8:c.*680A>G

ENST00000616242.5:c.682A>G

ENST00000345378.7:c.685A>G

ENST00000403799.8:c.682A>G

ENST00000671824.1:c.682A>G

ENST00000673284.1:c.682A>G

ENST00000345378.6:c.685A>G

ENST00000395796.7:c.679A>G

ENST00000403799.7:c.682A>G

ENST00000437084.1:c.631A>G

ENST00000616242.4:c.679A>G

NM_000162.3:c.682A>G

NM_033507.1:c.685A>G

NM_033508.1:c.679A>G

NM_000162.4:c.682A>G

NM_001354800.1:c.682A>G

NM_033507.2:c.685A>G

NM_033508.2:c.679A>G

NM_033507.3:c.685A>G

NM_033508.3:c.679A>G

Pathogenic

Met criteria codes **6**

PM2_Supporting

PS4

PP2

PP3

PM5_Supporting

PM1

Not Met criteria codes **1**

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.682A>G variant in the glucokinase gene, GCK, causes an amino acid change of threonine to alanine at codon 228 (p.(Thr228Ala)) 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 0.931 which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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). This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to 1 copy in the East Asian subpopulation and no copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in 7 unrelated individuals with hyperglycemia (PS4, PMIDs: 31638168, 12955723, internal lab contributors). Another missense variant, c.683C>T p.Thr228Met, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Thr228Ala (PM5_Supporting). In summary, c.682A>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, approved 8/11/2023): PM1, PP2, PP3, PM2_Supporting, PM5_Supporting, PS4.

Met criteria codes

PM2_Supporting			This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to 1 copy in the East Asian subpopulation and no copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).
PS4			This variant was identified in 7 unrelated individuals with hyperglycemia (PS4, PMIDs: 31638168, 12955723, 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 0.931 which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5_Supporting			Another missense variant, c.683C>T p.Thr228Met, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Thr228Ala (PM5_Supporting).
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).

Not Met criteria codes

PS3

While studies exploring the effect of this variant on protein function have been performed, these studies do not meet the criteria set forth by the MDEP for the application of PS3 or BS3 (PMID: 15752705).

Curation History

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