

Variant: NM_000162.5(GCK):c.622G>A (p.Ala208Thr)

Version: 1.2

CA367401322 [↗](#)

804344 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 7be4b009-9f38-4314-9c03-e3d5facd3f2d

Approved on: 2025/2/11

Published on: 2025/2/11

HGVS expressions

NM_000162.5(GCK):c.622G>A (p.Ala208Thr)

NM_000162.5:c.622G>A

NC_000007.14:g.44149817C>T

CM000669.2:g.44149817C>T

NC_000007.13:g.44189416C>T

CM000669.1:g.44189416C>T

NC_000007.12:g.44155941C>T

NG_008847.1:g.44607G>A

NG_008847.2:g.53354G>A

ENST00000395796.8:c.*620G>A

ENST00000616242.5:c.622G>A

ENST00000682635.1:n.1108G>A

ENST00000345378.7:c.625G>A

ENST00000403799.8:c.622G>A

ENST00000671824.1:c.622G>A

ENST00000673284.1:c.622G>A

ENST00000345378.6:c.625G>A

ENST00000395796.7:c.619G>A

ENST00000403799.7:c.622G>A

ENST00000437084.1:c.571G>A

ENST00000616242.4:c.619G>A

NM_000162.3:c.622G>A

NM_033507.1:c.625G>A

NM_033508.1:c.619G>A

NM_000162.4:c.622G>A

NM_001354800.1:c.622G>A

NM_033507.2:c.625G>A

NM_033508.2:c.619G>A

NM_033507.3:c.625G>A

NM_033508.3:c.619G>A

Pathogenic

Met criteria codes 9

PM3_Supporting

PS3_Moderate

PP1_Moderate

PS4_Moderate

PM5_Supporting

PM2_Supporting

PP2

PP3

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.622G>A variant in the glucokinase gene, GCK causes an amino acid change of Ala to Thr at codon 208 (p.(Ala208Thr)) 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 also predicted to be deleterious by computational evidence, with a REVEL score of 0.905, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an uncomputable Grpmax filtering allele frequency in the gnomAD v2.1.1 due to only one copy in the European non-Finnish population and no copies in another subpopulation (PM2_Supporting). This variant was identified in the heterozygous state in 5 unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors). This variant has been detected in the homozygous state in an individual with permanent neonatal diabetes (PM3_Supporting, PMID: 25015100). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3.0 mmol/L) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes/hyperglycemia with 3 informative meioses in 2 families (PP1_Moderate; PMID 25015100; internal lab contributors). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters passed the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Ala208Thr has RAI<0.50 (PS3_Moderate; PMID: 25015100). Another missense variant, c.623C>T p.Ala208Val, has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.Ala208Thr (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, approved 8/11/2023): PP3, PP2, PM2_Supporting, PP4_Moderate, PM5_Supporting, PS4_Moderate, PM3_Supporting, PP1_Moderate, PS3_Moderate.

Met criteria codes			
PM3_Supporting			This variant has been detected in the homozygous state in an individual with permanent neonatal diabetes (PM3_Supporting).
PS3_Moderate			A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Ala208Thr has RAI<0.50 (PS3_Moderate; PMID: 25015100).
PP1_Moderate			This variant segregated with diabetes with 3 informative meioses in 2 families (PP1_Moderate; PMID 25015100; internal lab contributors).
PS4_Moderate			This variant was identified in the heterozygous state in 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMID: internal lab contributors).
PM5_Supporting			

Another missense variant, c.623C>T p.Ala208Val, has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.Ala208Thr. (PM5_Supporting).

PM2_Supporting			This variant has an uncomputable Popmax filtering allele frequency in the gnomAD v2.1.1 due to only one copy in the European non-Finnish population and no copies in another subpopulation (PM2_Supporting).
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 0.905, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3.0 mmol/L) (PP4_Moderate; internal lab contributors).

Curation History

▼

▼

Showing 1 to 3 of 3 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.