

Variant: *NM_000162.5(GCK):c.661G>A (p.Glu221Lys)*

Version: 1.0

CA213824 [↗](#)

36241 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: bcac1d6c-8f3c-4870-ae6e-44213e7b972a

Approved on: 2024/2/28

Published on: 2024/2/28

HGVS expressions

NM_000162.5:c.661G>A

NM_000162.5(GCK):c.661G>A (p.Glu221Lys)

NC_000007.14:g.44149778C>T

CM000669.2:g.44149778C>T

NC_000007.13:g.44189377C>T

CM000669.1:g.44189377C>T

NC_000007.12:g.44155902C>T

NG_008847.1:g.44646G>A

NG_008847.2:g.53393G>A

ENST00000395796.8:c.*659G>A

ENST00000616242.5:c.661G>A

ENST00000682635.1:n.1147G>A

ENST00000345378.7:c.664G>A

ENST00000403799.8:c.661G>A

ENST00000671824.1:c.661G>A

ENST00000673284.1:c.661G>A

ENST00000345378.6:c.664G>A

ENST00000395796.7:c.658G>A

ENST00000403799.7:c.661G>A

ENST00000437084.1:c.610G>A

ENST00000616242.4:c.658G>A

NM_000162.3:c.661G>A

NM_033507.1:c.664G>A

NM_033508.1:c.658G>A

NM_000162.4:c.661G>A

NM_001354800.1:c.661G>A

NM_033507.2:c.664G>A

NM_033508.2:c.658G>A

NM_033507.3:c.664G>A

NM_033508.3:c.658G>A

Pathogenic

Met criteria codes 6

PP1_Strong

PS4

PP2

PP3

PM2_Supporting

PP4_Moderate

Not Met criteria codes 2

PS3

PM1

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			
<p>The c.661A>G variant in the glucokinase gene, GCK, causes an amino acid change of glutamic acid to lysine at codon 221 (p.(Glu221Lys)) 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 0.789, 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 is located in the larger hexokinase domain of the GCK gene (PMID: 31638168) but this variant does not reside in an amino acid that directly binds glucose or ATP, which is defined as critical for the protein’s function by the ClinGen MDEP. This variant was identified in 4 unrelated individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies or 2 hour OGTT glucose increment < 3 mmol/L) (PP4_Moderate; PMID: 23295292, internal lab contributors). This variant has been identified in 25 unrelated individuals with hyperglycemia and segregated with the phenotype, with 17 informative meioses in at least 7 families (PS4, PP1_Strong; PMIDs: 10694920, 12955723, 31658956, 34462253, 35592779, 35733065, 23295292, and 30592380). A relative activity index (RAI) was calculated for this variant but the wild type parameters are outside of MDEP's recommendations; therefore, this data cannot be used towards PS3 (PMID: 30592380). In summary, c.661A>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): PS4, PP1_Strong, PP4_Moderate, PP2, PP3, PM2_Supporting.</p>			
Met criteria codes			
PP1_Strong			This variant segregated with hyperglycemia, with 17 informative meioses in at least 7 families (PP1_Strong; PMIDs: 23295292, 30592380, 35733065, 10694920, internal lab contributors).
PS4			This variant was identified in 25 unrelated individuals with hyperglycemia (PS4; PMIDs: 10694920, 12955723, 31658956, 34462253, 35592779, 35733065, 23295292, and 30592380, 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 0.789, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate			

This variant was identified in 4 unrelated individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies or 2 hour OGTT increment < 3 mmol/L) (PP4_Moderate; PMID: 23295292, internal lab contributors).

Not Met criteria codes

PS3			A relative activity index (RAI) was calculated for this variant but the wild type parameters are outside of MDEP's recommendations; therefore, this data cannot be used towards PS3.
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

▼

▼

Showing 1 to 1 of 1 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.