

Variant: NM_033508.3:c.779G>A

Version: 1.0

CA367400569 [↗](#)

2578353 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 9ff98b1f-698d-45f3-a3d8-f835ad13f5a5

Approved on: 2023/8/12

Published on: 2023/8/12

HGVS expressions

NM_033508.3:c.779G>A

NC_000007.14:g.44147731C>T

CM000669.2:g.44147731C>T

NC_000007.13:g.44187330C>T

CM000669.1:g.44187330C>T

NC_000007.12:g.44153855C>T

NG_008847.1:g.46693G>A

NG_008847.2:g.55440G>A

ENST00000395796.8:c.*780G>A

ENST00000616242.5:c.782G>A

ENST00000345378.7:c.785G>A

ENST00000403799.8:c.782G>A

ENST00000671824.1:c.782G>A

ENST00000673284.1:c.782G>A

ENST00000345378.6:c.785G>A

ENST00000395796.7:c.779G>A

ENST00000403799.7:c.782G>A

ENST00000437084.1:c.731G>A

ENST00000616242.4:c.779G>A

NM_000162.3:c.782G>A

NM_033507.1:c.785G>A

NM_033508.1:c.779G>A

NM_000162.4:c.782G>A

NM_001354800.1:c.782G>A

NM_033507.2:c.785G>A

NM_033508.2:c.779G>A

NM_000162.5:c.782G>A

NM_033507.3:c.785G>A

Pathogenic

Met criteria codes **7**

PM2_Supporting

PS3_Moderate

PP1_Strong

PS4

PP2

PP3

PM5_Supporting

Not Met criteria codes **1**

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.782G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to glutamic acid at codon 261 (p.(Gly261Glu)) 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 0.989, which is greater than the MDEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). This variant was identified in more than 11 unrelated individuals with diabetes/hyperglycemia (PS4; PMID 19358091, 8168652 , internal lab contributors). This variant segregated with diabetes/hyperglycemia with 11 informative meioses in 4 families (PP1_Strong; internal lab contributors). 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.Gly261Glu variant has a relative activity index (RAI) of 0, which is less than the MDEP VCEP threshold of 0.50 (PMID: 19903754). Another missense variant, c.781G>A, (p.Gly261Arg), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.Gly261Glu(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 1.3.0, approved 8/11/2023): PM2_Supporting, PP2, PP3, PM5_Supporting, PS4, PP1_Strong, PS3_Moderate.

Met criteria codes

PM2_Supporting			This variant is absent in the gnomAD v2.1.1 (PM2_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.Gly261Glu variant has a relative activity index (RAI) of 0, which is less than the MDEP VCEP threshold of 0.50 (PMID: 19903754).
PP1_Strong			This variant segregated with diabetes/hyperglycemia with 11 informative meioses in 4 families (PP1_Strong; internal lab contributors).
PS4			This variant was identified in more than 11 unrelated individuals with diabetes (PS4; PMID 19358091, 8168652 , 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 0.989, which is greater than the MDEP threshold of 0.70 (PP3).
PM5_Supporting			Another missense variant, c.781G>A, (p.Gly261Arg), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.(Gly261Glu). (PM5_Supporting)

Not Met criteria codes

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.