

Variant: NM_000162.5(GCK):c.1160C>A (p.Ala387Glu)

Version: 1.1

CA213725 [↗](#)

36181 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 6d8941fd-d5e3-465b-9e80-eceefd70894e

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HGVS expressions

NM_000162.5:c.1160C>A

NM_000162.5(GCK):c.1160C>A (p.Ala387Glu)

NC_000007.14:g.44145590G>T

CM000669.2:g.44145590G>T

NC_000007.13:g.44185189G>T

CM000669.1:g.44185189G>T

NC_000007.12:g.44151714G>T

NG_008847.1:g.48834C>A

NG_008847.2:g.57581C>A

ENST00000395796.8:c.*1158C>A

ENST00000616242.5:c.*280C>A

ENST00000683378.1:n.386C>A

ENST00000336642.9:c.194C>A

ENST00000345378.7:c.1163C>A

ENST00000403799.8:c.1160C>A

ENST00000671824.1:c.1223C>A

ENST00000672743.1:n.172C>A

ENST00000673284.1:c.1160C>A

ENST00000336642.8:c.212C>A

ENST00000345378.6:c.1163C>A

ENST00000395796.7:c.1157C>A

ENST00000403799.7:c.1160C>A

ENST00000437084.1:c.1109C>A

ENST00000459642.1:n.540C>A

ENST00000616242.4:c.1157C>A

NM_000162.3:c.1160C>A

NM_033507.1:c.1163C>A

NM_033508.1:c.1157C>A

NM_000162.4:c.1160C>A

NM_001354800.1:c.1160C>A

NM_001354801.1:c.149C>A

NM_001354802.1:c.20C>A

NM_001354803.1:c.194C>A

NM_033507.2:c.1163C>A

NM_033508.2:c.1157C>A

NM_033507.3:c.1163C>A

NM_033508.3:c.1157C>A

Likely Pathogenic**Met criteria codes** 5

PM2_Supporting

PM5_Strong

PP2

PP3

PP4

Not Met criteria codes 2

PS4

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 1.3.0*
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1160C>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to glutamic acid at codon 387 (p.(Ala387Glu)) of NM_000162.5. This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to one copy in the European non-Finnish 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). 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 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, so it does not meet PM1. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.958 which is greater than the MDEP VCEP threshold of 0.70 (PP3). Two other missense variants, c.1159G>A p.(Ala387Thr) and c.1160C>T p.(Ala387Val) have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong). 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%) (PP4; internal lab contributors). In summary, c.1160C>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (VCEP specifications version v1.3.0; approved 8/11/2023): PP2, PP3, PM2_Supporting, PP4, PM5_Strong.

Met criteria codes**PM2_Supporting**

This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to one copy in the European non-Finnish 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).

PM5_Strong

Two other missense variants, c.1159G>A p.(Ala387Thr) and c.1160C>T p.(Ala387Val) have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong).

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

REVEL 0.958

PP4			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%) (PP4; internal lab contributors).
Not Met criteria codes			
PS4			This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (Internal lab contributors).
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 			
			▼ ▼
Showing 1 to 2 of 2 rows			

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