The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000162.5(GCK):c.1087G>A (p.Asp363Asn)

Version: 1.1

CA16618466

418228 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 91bdc867-15f1-4bc5-842f-c7d56ac49e83
Approved on: 2025/3/5
Published on: 2025/3/5

HGVS expressions

NM_000162.5(GCK):c.1087G>A (p.Asp363Asn)
NM_000162.5:c.1087G>A
NC_000007.14:g.44145663C>T
CM000669.2:g.44145663C>T
NC_000007.13:g.44185262C>T
CM000669.1:g.44185262C>T
NC_000007.12:g.44151787C>T
NG_008847.1:g.48761G>A
NG_008847.2:g.57508G>A
ENST00000395796.8:c.*1085G>A
ENST00000616242.5:c.*207G>A
ENST00000683378.1:n.313G>A
ENST00000336642.9:c.121G>A
ENST00000345378.7:c.1090G>A
ENST00000403799.8:c.1087G>A
ENST00000671824.1:c.1150G>A
ENST00000672743.1:n.99G>A
ENST00000673284.1:c.1087G>A
ENST00000336642.8:c.139G>A
ENST00000345378.6:c.1090G>A
ENST00000395796.7:c.1084G>A
ENST00000403799.7:c.1087G>A
ENST00000437084.1:c.1036G>A
ENST00000459642.1:n.467G>A
ENST00000473353.1:n.385G>A
ENST00000616242.4:c.1084G>A
NM_000162.3:c.1087G>A
NM_033507.1:c.1090G>A
NM_033508.1:c.1084G>A
NM_000162.4:c.1087G>A
NM_001354800.1:c.1087G>A
NM_001354801.1:c.76G>A
NM_001354802.1:c.-54G>A
NM_001354803.1:c.121G>A
NM_033507.2:c.1090G>A
NM_033508.2:c.1084G>A
NM_033507.3:c.1090G>A

NM_033508.3:c.1084G>A
NM_001354803.2:c.121G>A

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 3

PP1 PM1 PS4

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 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1087G>A variant in the glucokinase gene, GCK, causes an amino acid change of aspartic acid to asparagine at codon 363 (p.(Asp363Asn)) of NM_000162.5. This variant was identified in at least 1 individual with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs:19790256, 36257325, internal lab contributor). The individual had a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%, negative antibodies, and three-generation, dominant family history of diabetes (in a family not used for PP1)) (PP4_Moderate; internal lab contributor).This variant is absent from gnomAD v2.1.1 (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 predicted to be deleterious by computational evidence, with a REVEL score of 0.869, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Another missense variant, c.1088A>G (p.Asp363Gly), has been classified as pathogenic by the ClinGen MDEP but has a larger Grantham distance than p.(Asp363Asn) (PM5_Supporting). In summary, c.1087G>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP4_Moderate, PM2_Supporting, PP2, PP3, PM5_Supporting.

Met criteria codes

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.
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.869, which is greater than the MDEP VCEP threshold of 0.70.
PP4_Moderate	✔	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%, negative antibodies, and a three-generation, dominant family history of diabetes/hyperglycemia (in a family not used for PP1) (PP4_Moderate, internal lab contributor).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1. (PM2_Supporting)
PM5_Supporting	✔	

Another missense variant, c.1088A>G (p.Asp363Gly), has been classified as pathogenic by the ClinGen MDEP but has a larger Grantham distance than p.(Asp363Asn) (PM5_Supporting).

Not Met criteria codes

PP1	✖	This variant segregated with diabetes with one informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors).
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant was identified in at least 1 individual with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs:19790256, 36257325, internal lab contributor).

Curation History

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