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_033508.3:c.455C>A

Version: 2.0

CA367401917

2567920 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: dc0a8035-6e5a-4c6f-9c2e-bdda0a027ad3
Approved on: 2026/6/24
Published on: 2026/6/24

HGVS expressions

NM_033508.3:c.455C>A
NC_000007.14:g.44150981G>T
CM000669.2:g.44150981G>T
NC_000007.13:g.44190580G>T
CM000669.1:g.44190580G>T
NC_000007.12:g.44157105G>T
NG_008847.1:g.43443C>A
NG_008847.2:g.52190C>A
ENST00000395796.8:c.*456C>A
ENST00000616242.5:c.458C>A
ENST00000682635.1:n.944C>A
ENST00000345378.7:c.461C>A
ENST00000403799.8:c.458C>A
ENST00000671824.1:c.458C>A
ENST00000673284.1:c.458C>A
ENST00000345378.6:c.461C>A
ENST00000395796.7:c.455C>A
ENST00000403799.7:c.458C>A
ENST00000437084.1:c.407C>A
ENST00000616242.4:c.455C>A
NM_000162.3:c.458C>A
NM_033507.1:c.461C>A
NM_033508.1:c.455C>A
NM_000162.4:c.458C>A
NM_001354800.1:c.458C>A
NM_033507.2:c.461C>A
NM_033508.2:c.455C>A
NM_000162.5:c.458C>A
NM_033507.3:c.461C>A

Pathogenic

Met criteria codes 7

PM2_Supporting PP2 PP3 PM1 PM5 PS4_Moderate PP1_Strong

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PP4

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.458C>A variant in the glucokinase gene, GCK, causes an amino acid change of proline to histidine at codon 153 (p.(Pro153His)) 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 0.985, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). This variant is absent from gnomAD 4.1.0 (PM2_Supporting). This variant was identified in five unrelated individuals with hyperglycemia; however PP4 was unable to be evaluated due to insufficient clinical information (PS4_Moderate; internal lab contributors). This variant was segregated with hyperglycemia, with seven informative meioses in five families (PP1_Strong; internal lab contributors). Another missense variant at the same residue, c.457C>T (p.Pro153Ser), has been interpreted as pathogenic by the ClinGen MDEP, and p.Pro153His has a greater Grantham distance (PM5). In summary, c.458C>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0., approved 10/10/2025): PP1_Strong, PS4_Moderate, PM1, PM5, PM2_Supporting, PP2, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (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 0.985, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM1	✔	This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
PM5	✔	Another missense variant at the same residue, c.457C>T (p.Pro153Ser), has been interpreted as pathogenic by the ClinGen MDEP, and p.Pro153His has a greater Grantham distance (PM5).
PS4_Moderate	✔	This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors).
PP1_Strong	✔	This variant was segregated with hyperglycemia, with seven informative meioses in five families (PP1_Strong; internal lab contributors).

Not Met criteria codes

PP4		✖	This variant was identified in 5 unrelated individuals with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors).

Curation History

Showing 1 to 2 of 2 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.

ClinGen Terms of Use.

¤ Powered by BCM's Genboree.