

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

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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**

PM1 PM5 PP1_Strong
PS4_Moderate PM2_Supporting PP2
PP3

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Not Met criteria codes 1

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

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).
PP1_Strong			This variant was segregated with hyperglycemia, with seven informative meioses in five families (PP1_Strong; internal lab contributors).
PS4_Moderate			This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors).
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).

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

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