

Variant: *NM\_033508.3:c.458T>G*

Version: 1.0

CA367401907 [↗](#)

2682650 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** 68140ef7-889c-4017-aacc-dd8c9fb840ca

**Approved on:** 2023/12/8

**Published on:** 2023/12/8

### *HGVS expressions*

#### **NM\_033508.3:c.458T>G**

NC\_000007.14:g.44150978A>C  
CM000669.2:g.44150978A>C  
NC\_000007.13:g.44190577A>C  
CM000669.1:g.44190577A>C  
NC\_000007.12:g.44157102A>C  
NG\_008847.1:g.43446T>G  
NG\_008847.2:g.52193T>G  
ENST00000395796.8:c.\*459T>G  
ENST00000616242.5:c.461T>G  
ENST00000682635.1:n.947T>G  
ENST00000345378.7:c.464T>G  
ENST00000403799.8:c.461T>G  
ENST00000671824.1:c.461T>G  
ENST00000673284.1:c.461T>G  
ENST00000345378.6:c.464T>G  
ENST00000395796.7:c.458T>G  
ENST00000403799.7:c.461T>G  
ENST00000437084.1:c.410T>G  
ENST00000616242.4:c.458T>G  
NM\_000162.3:c.461T>G  
NM\_033507.1:c.464T>G  
NM\_033508.1:c.458T>G  
NM\_000162.4:c.461T>G  
NM\_001354800.1:c.461T>G  
NM\_033507.2:c.464T>G  
NM\_033508.2:c.458T>G  
NM\_000162.5:c.461T>G  
NM\_033507.3:c.464T>G

**Likely Pathogenic**

Met criteria codes **5**

PP2 PP3 PM2\_Supporting  
PS2\_Moderate PP4\_Moderate

Evidence Links **0**

Expert Panel

Monogenic Diabetes VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.461T>G variant in the glucokinase gene, GCK, causes an amino acid change of valine to glycine at codon 154 (p.(Val154Gly)) of NM\_000162.5. 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% and negative antibodies) (PP4\_Moderate; internal lab contributors). This variant was identified as a de novo occurrence with unconfirmed parental relationships in an individual with diabetes, whose clinical picture is highly specific for GCK-hyperglycemia (PS2\_Moderate; internal lab contributor). 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 0.953, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2\_Supporting). In summary, c.461T>G 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, PS2\_Moderate, PP2, PP3, PM2\_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 (PP2).                                                   |
| PP3            |  |  | This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.953, which is greater than the MDEP VCEP threshold of 0.70 (PP3).                                                             |
| PM2_Supporting |  |  | This variant is absent in gnomAD v2.1.1 (PM2_Supporting).                                                                                                                                                                    |
| PS2_Moderate   |  |  | This variant was identified as a de novo occurrence with unconfirmed parental relationships in an individual with diabetes, whose clinical picture is highly specific for GCK-MODY (PS2_Moderate) internal lab contributor). |
| 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% and negative antibodies) (PP4_Moderate; internal lab contributors).        |

Curation History [↗](#)

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