

Variant: NM_000162.5(GCK):c.1114G>T (p.Glu372Ter)

Version: 1.0

CA213711 [↗](#)

36174 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 77a3bf59-08d2-4712-8073-89691ff3c35a

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HGVS expressions

NM_000162.5:c.1114G>T

NM_000162.5(GCK):c.1114G>T (p.Glu372Ter)

NC_000007.14:g.44145636C>A

CM000669.2:g.44145636C>A

NC_000007.13:g.44185235C>A

CM000669.1:g.44185235C>A

NC_000007.12:g.44151760C>A

NG_008847.1:g.48788G>T

NG_008847.2:g.57535G>T

ENST00000395796.8:c.*1112G>T

ENST00000616242.5:c.*234G>T

ENST00000683378.1:n.340G>T

ENST00000336642.9:c.148G>T

ENST00000345378.7:c.1117G>T

ENST00000403799.8:c.1114G>T

ENST00000671824.1:c.1177G>T

ENST00000672743.1:n.126G>T

ENST00000673284.1:c.1114G>T

ENST00000336642.8:c.166G>T

ENST00000345378.6:c.1117G>T

ENST00000395796.7:c.1111G>T

ENST00000403799.7:c.1114G>T

ENST00000437084.1:c.1063G>T

ENST00000459642.1:n.494G>T

ENST00000616242.4:c.1111G>T

NM_000162.3:c.1114G>T

NM_033507.1:c.1117G>T

NM_033508.1:c.1111G>T

NM_000162.4:c.1114G>T

NM_001354800.1:c.1114G>T

NM_001354801.1:c.103G>T

NM_001354802.1:c.-27G>T

NM_001354803.1:c.148G>T

NM_033507.2:c.1117G>T

NM_033508.2:c.1111G>T

NM_033507.3:c.1117G>T

NM_033508.3:c.1111G>T

Likely Pathogenic**Met criteria codes** **2****PVS1** **PM2_Supporting****Not Met criteria codes** **2****PS4** **PP4****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 1.2.0*
-  **Criteria Specification Approval History**
-  **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1114G>T variant in the glucokinase gene, GCK, results in a premature termination at codon 372 (p.Glu372Ter) of NM_000162.5. While this variant, located in exon 9 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 22335469, ClinVar ID: 36174, internal lab contributor). Two of these individuals had a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (PMID: 22335469, internal lab contributor). In summary, c.1114G>T 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): PVS1, PM2_supporting.

Met criteria codes

- | | | | |
|-----------------------|---|---|--|
| PVS1 |  |  | This variant, located in biologically-relevant exon 9 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). |
| PM2_Supporting |  |  | This variant is absent from gnomAD v2.1.1 (PM2_Supporting). |

Not Met criteria codes

- | | | | |
|------------|---|---|---|
| PS4 |  |  | This variant was identified in 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 22335469, ClinVar ID: 36174, internal lab contributor). |
| PP4 |  |  | This variant was identified in 2 individuals with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (PMID: 22335469, internal lab contributor). |



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