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Variant: NM_000162.5(GCK):c.98T>A (p.Val33Glu)

Version: 1.0

CA367403606

435309 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 3f0283f1-d408-433d-a871-21918fd3bf85
Approved on: 2026/4/17
Published on: 2026/6/24

HGVS expressions

NM_000162.5(GCK):c.98T>A (p.Val33Glu)
NM_000162.5:c.98T>A
NC_000007.14:g.44153411A>T
CM000669.2:g.44153411A>T
NC_000007.13:g.44193010A>T
CM000669.1:g.44193010A>T
NC_000007.12:g.44159535A>T
NG_008847.1:g.41013T>A
NG_008847.2:g.49760T>A
ENST00000395796.8:c.*96T>A
ENST00000616242.5:c.98T>A
ENST00000682635.1:n.584T>A
ENST00000345378.7:c.101T>A
ENST00000403799.8:c.98T>A
ENST00000671824.1:c.98T>A
ENST00000673284.1:c.98T>A
ENST00000345378.6:c.101T>A
ENST00000395796.7:c.95T>A
ENST00000403799.7:c.98T>A
ENST00000437084.1:c.98T>A
ENST00000476008.1:n.533T>A
ENST00000616242.4:c.95T>A
NM_000162.3:c.98T>A
NM_033507.1:c.101T>A
NM_033508.1:c.95T>A
NM_000162.4:c.98T>A
NM_001354800.1:c.98T>A
NM_033507.2:c.101T>A
NM_033508.2:c.95T>A
NM_033507.3:c.101T>A
NM_033508.3:c.95T>A

Uncertain Significance

Met criteria codes 4

PM2_Supporting PM5_Supporting PP2 PP3

Expert Panel

Monogenic Diabetes VCEP

Not Met criteria codes 2

PS4 PP4

Evidence Links 0

Criteria Specification Information

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.98T>A variant in the glucokinase gene, GCK, causes an amnio acid change of valine to glutamate at codon 33 (p.(Val33Glu)) of NM_000162.5. This variant is absent from gnomAD v4.1.0 (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 0.97, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Another missense variant at the same residue, c.98T>C (p.Val33Ala), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). This variant was identified in two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (ClinVar, internal lab contributors). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors). In summary, c.98T>A meets the criteria to be classified as uncertain significance for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PM2_Supporting, PP2, PP3, PM5_supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant at the same residue, c.98T>C (p.Val33Ala), has been classified as likely pathogenic by the ClinGen MDEP (PM5_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 0.97, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

PS4	✖	This variant was identified in two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (ClinVar, internal lab contributors).
PP4	✖	This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors).

Curation History

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