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Variant: NM_000162.5(GCK):c.106C>T (p.Arg36Trp)

Version: 2.0

CA4239720

431973 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 2bd76ae9-5b63-4964-b20a-1ac96ac6e398
Approved on: 2026/2/11
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HGVS expressions

NM_000162.5:c.106C>T
NM_000162.5(GCK):c.106C>T (p.Arg36Trp)
NC_000007.14:g.44153403G>A
CM000669.2:g.44153403G>A
NC_000007.13:g.44193002G>A
CM000669.1:g.44193002G>A
NC_000007.12:g.44159527G>A
NG_008847.1:g.41021C>T
NG_008847.2:g.49768C>T
ENST00000395796.8:c.*104C>T
ENST00000616242.5:c.106C>T
ENST00000682635.1:n.592C>T
ENST00000345378.7:c.109C>T
ENST00000403799.8:c.106C>T
ENST00000671824.1:c.106C>T
ENST00000673284.1:c.106C>T
ENST00000345378.6:c.109C>T
ENST00000395796.7:c.103C>T
ENST00000403799.7:c.106C>T
ENST00000437084.1:c.106C>T
ENST00000476008.1:n.541C>T
ENST00000616242.4:c.103C>T
NM_000162.3:c.106C>T
NM_033507.1:c.109C>T
NM_033508.1:c.103C>T
NM_000162.4:c.106C>T
NM_001354800.1:c.106C>T
NM_033507.2:c.109C>T
NM_033508.2:c.103C>T
NM_033507.3:c.109C>T
NM_033508.3:c.103C>T

Pathogenic

Met criteria codes 5

PP1_Strong PS2_Moderate PP2 PP3 PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

Not Met criteria codes 7

PM2 BA1 BS1 BS3 BP4 PS3 PS4

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.106C>T variant in the glucokinase gene,GCK, causes an amino acid change of arginine to tryptophan at codon 36 (p.(Arg36Trp)) 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 0.911, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has a Grpmax filtering allele frequency of 0.00001064 in gnomAD v4.1.0, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied, and thus PS4 cannot be applied because the variant MAF in gnomAD is above the ClinGen MDEP PM2_Supporting cutoff. This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). Additionally, this variant was identified as a de novo occurrence with confirmed parental relationships in an individual with diabetes, but whose clinical picture is not highly specific for GCK-MODY (PS2_Moderate; PMID: 8168652). This variant segregated with diabetes, with eight informative meioses in four families with MODY (PP1_Strong; PMIDs: 17573900, 23433541, 33477506, internal lab contributors). In summary, c.106C>T 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): PP2, PP3, PP4_Moderate, PS2_Moderate, PP1_Strong,

Met criteria codes

PP1_Strong	✔	This variant segregated with hyperglycemia with eight informative meioses in four families (PMIDs: 17573900, 23433541, 33477506, internal lab contributors).
PS2_Moderate	✔	This variant was identified as a de novo occurrence with confirmed parental relationships in an individual with diabetes, but whose clinical picture is not highly specific for GCK-MODY (PS2_Moderate; PMID: 8168652).
PP2	✔	gnomAD missense constraint score for GCK is 4.39, which is significant.
PP3	✔	REVEL=0.911>0.7
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors).

Not Met criteria codes

PM2	✖	This variant has a Grpmax filtering allele frequency of 0.00001064 in gnomAD v4.1.0, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied.

BA1		✖	gnomAD v2.1.1 Popmax Filtering AF 0.000002920 <0.0001
BS1		✖	This variant has a Grpmax filtering allele frequency of 0.00001064 in gnomAD v4.1.0, which falls between ClinGen MDEP-established cutoffs for PM2_Supporting and BS1; thus, neither criterion will be applied.
BS3		✖	Miller 1999 (PMID:10426385) reported Arg36Trp GCK had similar kinetic property as wildtype (Vmax and S0.5), and normal thermal stability, but proposed possible damage to interaction with GLUT2. GKRP/GKA binding studies not done.
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	Miller 1999 (PMID:10426385) reported Arg36Trp GCK had similar kinetic property as wildtype (Vmax and S0.5), and normal thermal stability, but proposed possible damage to interaction with GLUT2. GKRP/GKA binding studies not done.
PS4		✖	No PS4 at any level if not met PM2_Supporting

Curation History

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