

Variant: *NM_000162.5(GCK):c.469G>A (p.Glu157Lys)*

Version: 1.0

CA367401880 [↗](#)

447402 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: f1e69474-bfa1-497c-9917-b837d2476def

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HGVS expressions

NM_000162.5(GCK):c.469G>A (p.Glu157Lys)

NM_000162.5:c.469G>A

NC_000007.14:g.44150970C>T

CM000669.2:g.44150970C>T

NC_000007.13:g.44190569C>T

CM000669.1:g.44190569C>T

NC_000007.12:g.44157094C>T

NG_008847.1:g.43454G>A

NG_008847.2:g.52201G>A

ENST00000395796.8:c.*467G>A

ENST00000616242.5:c.469G>A

ENST00000682635.1:n.955G>A

ENST00000345378.7:c.472G>A

ENST00000403799.8:c.469G>A

ENST00000671824.1:c.469G>A

ENST00000673284.1:c.469G>A

ENST00000345378.6:c.472G>A

ENST00000395796.7:c.466G>A

ENST00000403799.7:c.469G>A

ENST00000437084.1:c.418G>A

ENST00000616242.4:c.466G>A

NM_000162.3:c.469G>A

NM_033507.1:c.472G>A

NM_033508.1:c.466G>A

NM_000162.4:c.469G>A

NM_001354800.1:c.469G>A

NM_033507.2:c.472G>A

NM_033508.2:c.466G>A

NM_033507.3:c.472G>A

NM_033508.3:c.466G>A

Pathogenic

Met criteria codes 6

PS4PP2PP4_ModeratePM2_SupportingPP1_StrongPS3_Moderate

Not Met criteria codes 3

PP3PM1BP4

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 3.1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.469G>A variant in the glucokinase gene, GCK, results in an amino acid substitution of glutamic acid to lysine at codon 157 (p.(Glu157Lys)) of NM_000162.5. The variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to no more than one copy in any subpopulation (PM2_Supporting). GCK is defined by the ClinGen Monogenic Diabetes Expert Panel (MDEP) as a gene with a low rate of benign missense variation in which missense variants are a common disease mechanism (PP2). Functional studies meeting MDEP wild type quality control measures demonstrated that this variant has a relative activity Index (RAI) of 0.08, which is below the MDEP cutoff (<0.5) (PS3_Moderate; PMID: 41516031). The variant was identified in at least 32 individuals with hyperglycemia (PS4; PMIDs: 11508276/28726111, 16602010, 29056535, 35737141, 36257325, internal lab contributors). Furthermore, at least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (pediatric case with fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative) (PP4_Moderate; internal lab contributors). Co-segregation analysis across multiple families demonstrated at least thirteen informative meioses in which the variant segregated with hyperglycemia (PP1_Strong; PMID: 11508276/28726111; internal lab contributors). In summary, c.469G>A (p.(Glu157Lys)) meets criteria to be classified as Pathogenic for monogenic diabetes, ACMG/AMP criteria applied, as specified by the ClinGen Monogenic Diabetes VCEP (GCK specification v3.1.0): PP1_Strong, PP2, PP4_Moderate, PM2_Supporting, PS3_Moderate, PS4.

Met criteria codes

PS4		✓	This variant was identified in at least 32 individuals with hyperglycemia (PS4; PMID: 11508276/28726111, 16602010, 29056535, 35737141, 36257325, internal lab contributors).
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).
PP4_Moderate		✓	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (pediatric case with fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4_Moderate; internal lab contributors).
PM2_Supporting		✓	This variant has an incomputable gnomAD v4.1.0 Grpmax filtering allele frequency due to the presence of no more than one copy in any subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (Grpmax FAF <= 0.000003) (PM2_Supporting).
PP1_Strong		✓	This variant segregated with hyperglycemia with at least 13 informative meioses in multiple families (PP1_Strong; PMID: 28726111; internal lab contributors).
PS3_Moderate		✓	



MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.08, which is below the MDEP cutoff (PS3_Moderate; PMID: 41516031).

Not Met criteria codes

PP3



This variant has a REVEL score of 0.688, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function.

PM1



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4



This variant has a REVEL score of 0.688, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function.

Curation History

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