

Variant: NM_000162.5(GCK):c.1345G>A (p.Ala449Thr)

Version: 1.0

CA213758 [↗](#)

36199 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: cacf5183-a9c7-4f46-b4f0-96850253a67d

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HGVS expressions

NM_000162.5(GCK):c.1345G>A (p.Ala449Thr)

NM_000162.5:c.1345G>A

NC_000007.14:g.44145189C>T

CM000669.2:g.44145189C>T

NC_000007.13:g.44184788C>T

CM000669.1:g.44184788C>T

NC_000007.12:g.44151313C>T

NG_008847.1:g.49235G>A

NG_008847.2:g.57982G>A

ENST00000395796.8:c.*1343G>A

ENST00000616242.5:c.*465G>A

ENST00000683378.1:n.571G>A

ENST00000336642.9:c.379G>A

ENST00000345378.7:c.1348G>A

ENST00000403799.8:c.1345G>A

ENST00000671824.1:c.1408G>A

ENST00000672743.1:n.357G>A

ENST00000673284.1:c.1345G>A

ENST00000336642.8:c.397G>A

ENST00000345378.6:c.1348G>A

ENST00000395796.7:c.1342G>A

ENST00000403799.7:c.1345G>A

ENST00000437084.1:c.1294G>A

ENST00000459642.1:n.725G>A

ENST00000616242.4:c.1342G>A

NM_000162.3:c.1345G>A

NM_033507.1:c.1348G>A

NM_033508.1:c.1342G>A

NM_000162.4:c.1345G>A

NM_001354800.1:c.1345G>A

NM_001354801.1:c.334G>A

NM_001354802.1:c.205G>A

NM_001354803.1:c.379G>A

NM_033507.2:c.1348G>A

NM_033508.2:c.1342G>A

NM_033507.3:c.1348G>A

NM_033508.3:c.1342G>A

Pathogenic

Met criteria codes 8

- PS3_Supporting
- PP1_Strong
- PM2_Supporting
- PS4_Moderate
- PM3
- PP2
- PP3
- PP4

Not Met criteria codes 1

- PM1

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 1.3.0
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1345G>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to threonine at codon 449 (p.(Ala449Thr)) 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 0.89, which is greater than the MDEP VCEP threshold of 0.70 (PP3). While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the relative stability index was below the MDEP cutoff of 0.5 (PS3_Supporting; PMID: 25015100). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 25015100, internal lab contributors). This variant has been detected in the homozygous state in 3 individuals with permanent neonatal diabetes (PNDM) and negative testing for ABCC8, KCNJ11, and INS (PM3). This variant segregated in the homozygous state with permanent neonatal diabetes and the in the heterozygous state with hyperglycemia, with 6 informative meioses in 2 families (PP1_Strong; internal lab contributors). In summary, c.1345G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_Strong, PM3, PS4_Moderate, PP2, PP3, PP4, PM2_Moderate, PS3_Supporting.

Met criteria codes

PS3_Supporting		✓	While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the relative stability index was below the MDEP cutoff of 0.5 (PS3_Supporting; PMID: 25015100).
PP1_Strong		✓	This variant segregated in the homozygous state with permanent neonatal diabetes and the in the heterozygous state with hyperglycemia, with 6 informative meioses in 2 families (PP1_Strong; internal lab contributors).
PM2_Supporting		✓	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 1 copy in gnomAD 4.0, low coverage
PS4_Moderate		✓	This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 25015100, internal lab contributors).
PM3		✓	This variant has been detected in the homozygous state in 3 unrelated individuals with permanent neonatal diabetes (PM3; 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).
PP3			This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.89, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4			This variant was identified in in the homozygous state in 3 unrelated individual(s) and two of their siblings with neonatal diabetes and negative testing for ABCC8, KCNJ11, and INS (PP4; PMID: 25015100, internal lab contributors).
Not Met criteria codes			
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 			
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