

Variant: NM_000162.5(GCK):c.370G>A (p.Asp124Asn)

Version: 1.0

CA206547 [↗](#)

211073 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: e92e139f-6994-4774-beb3-99278185204a

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HGVS expressions

NM_000162.5(GCK):c.370G>A (p.Asp124Asn)

NM_000162.5:c.370G>A

NC_000007.14:g.44151069C>T

CM000669.2:g.44151069C>T

NC_000007.13:g.44190668C>T

CM000669.1:g.44190668C>T

NC_000007.12:g.44157193C>T

NG_008847.1:g.43355G>A

NG_008847.2:g.52102G>A

ENST00000395796.8:c.*368G>A

ENST00000616242.5:c.370G>A

ENST00000682635.1:n.856G>A

ENST00000345378.7:c.373G>A

ENST00000403799.8:c.370G>A

ENST00000671824.1:c.370G>A

ENST00000673284.1:c.370G>A

ENST00000345378.6:c.373G>A

ENST00000395796.7:c.367G>A

ENST00000403799.7:c.370G>A

ENST00000437084.1:c.364-45G>A

ENST00000616242.4:c.367G>A

NM_000162.3:c.370G>A

NM_033507.1:c.373G>A

NM_033508.1:c.367G>A

NM_000162.4:c.370G>A

NM_001354800.1:c.370G>A

NM_033507.2:c.373G>A

NM_033508.2:c.367G>A

NM_033507.3:c.373G>A

NM_033508.3:c.367G>A

Pathogenic

Met criteria codes 6

PP1_StrongPP4_ModeratePP2PP3PS4PM2_Supporting

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 1.2.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP			
<p>The c.370G>A variant in the glucokinase gene, GCK, causes an amino acid change of aspartic acid to asparagine at codon 124 (p. (Asp124Asn)) 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 0.817, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to one copy in the European non-Finnish subpopulation and one copy in the Latino/Admixed American subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in 14 unrelated individuals with hyperglycemia (PS4; PMIDs: 20337973, 22773699, internal lab contributors). This variant was identified in a at least three individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes/hyperglycemia, with seven informative meioses in five families (PP1_Strong; internal lab contributors). In summary, c.379G>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, PS4, PP4_Moderate, PP2, PP3, PM2_Supporting.</p>			
Met criteria codes			
PP1_Strong			This variant segregated with diabetes/hyperglycemia, with 6 informative meioses in 4 families (PP1_Strong; internal lab contributors).
PP4_Moderate			This variant was identified in a at least 3 individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT increment < 3 mmol/L) (PP4_Moderate; 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 0.817, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS4			This variant was identified in 14 unrelated individuals with hyperglycemia (PS4; PMIDs: 20337973, 22773699, internal lab contributors).
PM2_Supporting			



This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 1 copies in the Latino/Admixed American subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF ≤ 0.000003 and ≤ 2 copies in ENF and ≤ 1 copy in any other subpopulation) (PM2_Supporting).

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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