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Variant: NM_000162.5(GCK):c.1030G>T (p.Asp344Tyr)

Version: 1.0

CA279947

219179 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 29711798-f87c-4b3d-bba2-b5ac6add850c
Approved on: 2024/4/28
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HGVS expressions

NM_000162.5(GCK):c.1030G>T (p.Asp344Tyr)
NM_000162.5:c.1030G>T
NC_000007.14:g.44145720C>A
CM000669.2:g.44145720C>A
NC_000007.13:g.44185319C>A
CM000669.1:g.44185319C>A
NC_000007.12:g.44151844C>A
NG_008847.1:g.48704G>T
NG_008847.2:g.57451G>T
ENST00000395796.8:c.*1028G>T
ENST00000616242.5:c.*150G>T
ENST00000683378.1:n.256G>T
ENST00000336642.9:c.64G>T
ENST00000345378.7:c.1033G>T
ENST00000403799.8:c.1030G>T
ENST00000671824.1:c.1093G>T
ENST00000672743.1:n.42G>T
ENST00000673284.1:c.1030G>T
ENST00000336642.8:c.82G>T
ENST00000345378.6:c.1033G>T
ENST00000395796.7:c.1027G>T
ENST00000403799.7:c.1030G>T
ENST00000437084.1:c.979G>T
ENST00000459642.1:n.410G>T
ENST00000473353.1:n.328G>T
ENST00000616242.4:c.1027G>T
NM_000162.3:c.1030G>T
NM_033507.1:c.1033G>T
NM_033508.1:c.1027G>T
NM_000162.4:c.1030G>T
NM_001354800.1:c.1030G>T
NM_001354801.1:c.19G>T
NM_001354802.1:c.-111G>T
NM_001354803.1:c.64G>T
NM_033507.2:c.1033G>T
NM_033508.2:c.1027G>T
NM_033507.3:c.1033G>T

NM_033508.3:c.1027G>T
NM_001354803.2:c.64G>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP2 PP3 PP4_Moderate PM3_Supporting

Not Met criteria codes 2

PP1 PS4

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.1030G>T variant in the glucokinase gene, GCK, causes an amino acid change of aspartate to tyrosine at codon 344 (p.(Asp344Tyr)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (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 0.861, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in 2 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 27016322, internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT 2H increment < 3 mmol/L and negative antibodies) (PP4_Moderate; PMID: 27016322). This variant has been detected in the homozygous state in 1 individual with permanent neonatal diabetes (PM3_Supporting; internal lab contributors). This variant segregated with hyperglycemia with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 27016322). In summary, c.1165G>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP4_Moderate, PM2_supporting, PP2, PP3, PM3_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.0.0: 0 copy
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 0.861, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and OGTT 2H increment < 3 mmol/L and negative antibodies) (PP4_Moderate; PMID: 27016322).

PM3_Supporting		✔	This variant has been detected in the homozygous state in 1 individual with permanent neonatal diabetes (PM3_Supporting; internal lab contributors).

Not Met criteria codes

PP1		✖	This variant segregated with hyperglycemia with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 27016322).
PS4		✖	This variant was identified in 2 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (ClinVar ID:219179, internal lab contributors).

Curation History

Showing 1 to 1 of 1 rows

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