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Variant: NM_000162.5(GCK):c.1042A>T (p.Ile348Phe)

Version: 1.0

CA213707

36172 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: a2cd0e1b-7646-4d8c-bd26-f2e6b6a581ff
Approved on: 2024/1/28
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HGVS expressions

NM_000162.5(GCK):c.1042A>T (p.Ile348Phe)
NM_000162.5:c.1042A>T
NC_000007.14:g.44145708T>A
CM000669.2:g.44145708T>A
NC_000007.13:g.44185307T>A
CM000669.1:g.44185307T>A
NC_000007.12:g.44151832T>A
NG_008847.1:g.48716A>T
NG_008847.2:g.57463A>T
ENST00000395796.8:c.*1040A>T
ENST00000616242.5:c.*162A>T
ENST00000683378.1:n.268A>T
ENST00000336642.9:c.76A>T
ENST00000345378.7:c.1045A>T
ENST00000403799.8:c.1042A>T
ENST00000671824.1:c.1105A>T
ENST00000672743.1:n.54A>T
ENST00000673284.1:c.1042A>T
ENST00000336642.8:c.94A>T
ENST00000345378.6:c.1045A>T
ENST00000395796.7:c.1039A>T
ENST00000403799.7:c.1042A>T
ENST00000437084.1:c.991A>T
ENST00000459642.1:n.422A>T
ENST00000473353.1:n.340A>T
ENST00000616242.4:c.1039A>T
NM_000162.3:c.1042A>T
NM_033507.1:c.1045A>T
NM_033508.1:c.1039A>T
NM_000162.4:c.1042A>T
NM_001354800.1:c.1042A>T
NM_001354801.1:c.31A>T
NM_001354802.1:c.-99A>T
NM_001354803.1:c.76A>T
NM_033507.2:c.1045A>T
NM_033508.2:c.1039A>T
NM_033507.3:c.1045A>T

NM_033508.3:c.1039A>T
NM_001354803.2:c.76A>T

Likely Pathogenic

Met criteria codes 5

PM2 PP2 PP3 PP4 PS4_Moderate

Not Met criteria codes 2

PM1 PP1

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

The c.1042A>T variant in the glucokinase gene, GCK, causes an amino acid change of isoleucine to phenylalanine at codon 348 (p.(Ile348Phe)) 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 0.83, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 30386132 and 28095440, ClinVar ID:36172, internal lab contributors). One of these individual had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors). This variant segregated with diabetes with 1 informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 28095440). In summary, this variant meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PS4_Moderate, PP2, PP3, PP4, PM2_Supporting.

Met criteria codes

PM2	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
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 0.83, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4	✔	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%) (PP4; internal lab contributors).
PS4_Moderate	✔	This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 30386132 and 28095440, ClinVar ID:36172, 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
PP1	✖	This variant segregated with diabetes with 1 informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 28095440).

Curation History

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