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Variant: NM_000162.5(GCK):c.1270C>T (p.His424Tyr)

Version: 1.0

CA367397245

1709730 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e6f1f682-ee06-41f7-8019-403a85abf4ad
Approved on: 2023/11/23
Published on: 2023/11/23

HGVS expressions

NM_000162.5:c.1270C>T
NM_000162.5(GCK):c.1270C>T (p.His424Tyr)
NC_000007.14:g.44145264G>A
CM000669.2:g.44145264G>A
NC_000007.13:g.44184863G>A
CM000669.1:g.44184863G>A
NC_000007.12:g.44151388G>A
NG_008847.1:g.49160C>T
NG_008847.2:g.57907C>T
ENST00000395796.8:c.*1268C>T
ENST00000616242.5:c.*390C>T
ENST00000683378.1:n.496C>T
ENST00000336642.9:c.304C>T
ENST00000345378.7:c.1273C>T
ENST00000403799.8:c.1270C>T
ENST00000671824.1:c.1333C>T
ENST00000672743.1:n.282C>T
ENST00000673284.1:c.1270C>T
ENST00000336642.8:c.322C>T
ENST00000345378.6:c.1273C>T
ENST00000395796.7:c.1267C>T
ENST00000403799.7:c.1270C>T
ENST00000437084.1:c.1219C>T
ENST00000459642.1:n.650C>T
ENST00000616242.4:c.1267C>T
NM_000162.3:c.1270C>T
NM_033507.1:c.1273C>T
NM_033508.1:c.1267C>T
NM_000162.4:c.1270C>T
NM_001354800.1:c.1270C>T
NM_001354801.1:c.259C>T
NM_001354802.1:c.130C>T
NM_001354803.1:c.304C>T
NM_033507.2:c.1273C>T
NM_033508.2:c.1267C>T
NM_033507.3:c.1273C>T
NM_033508.3:c.1267C>T

NM_001354803.2:c.304C>T

Likely Pathogenic

Met criteria codes 6

PP2 PP3 PP1_Moderate PP4_Moderate PM2_Supporting PS4_Moderate

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.1270C>T variant in the glucokinase gene, GCK, causes an amino acid change of histidine to tyrosine at codon 424 (p.(His424Tyr)) 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 0.897, 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 6 unrelated individuals with hyperglycemia (PS4_Moderate; ClinVar: 1709730, PMIDs: 27726111, 22035297, 31595705 internal lab contributors), including 3 individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% as well as OGTT increment < 3 mmol/L and/or negative antibodies in untreated pediatric case) (PP4_Moderate; PMIDs: 19410318, 28726111, internal lab contributors). This variant segregated with hyperglycemia, with 4 informative meioses in 1 family (PP1_Moderate; PMIDs: 22035297). In summary, c.1270C>T 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, approved 8/11/2023): PP1_Moderate, PP4_Moderate, PS4_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

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 of0.897, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Moderate	✔	This variant segregated with hyperglycemia, with 4 informative meioses in 1 family (PP1_Moderate; PMIDs: 22035297).
PP4_Moderate	✔	This variant was identified in three individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% as well as OGTT increment < 3 mmol/L and/or negative antibodies in untreated pediatric case) (PP4_Moderate; PMIDs: 19410318, 28726111, internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

PS4_Moderate		✔	This variant was identified in 6 unrelated individuals with hyperglycemia (PS4_Moderate; ClinVar: 1709730, PMIDs: 27726111, 22035297, 31595705 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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