The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000162.5(GCK):c.1268T>A (p.Phe423Tyr)

Version: 1.0

CA213740

36189 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: fa69a74e-6d24-423d-a24e-3ea3241ed013
Approved on: 2024/4/27
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HGVS expressions

NM_000162.5(GCK):c.1268T>A (p.Phe423Tyr)
NM_000162.5:c.1268T>A
NC_000007.14:g.44145266A>T
CM000669.2:g.44145266A>T
NC_000007.13:g.44184865A>T
CM000669.1:g.44184865A>T
NC_000007.12:g.44151390A>T
NG_008847.1:g.49158T>A
NG_008847.2:g.57905T>A
ENST00000395796.8:c.*1266T>A
ENST00000616242.5:c.*388T>A
ENST00000683378.1:n.494T>A
ENST00000336642.9:c.302T>A
ENST00000345378.7:c.1271T>A
ENST00000403799.8:c.1268T>A
ENST00000671824.1:c.1331T>A
ENST00000672743.1:n.280T>A
ENST00000673284.1:c.1268T>A
ENST00000336642.8:c.320T>A
ENST00000345378.6:c.1271T>A
ENST00000395796.7:c.1265T>A
ENST00000403799.7:c.1268T>A
ENST00000437084.1:c.1217T>A
ENST00000459642.1:n.648T>A
ENST00000616242.4:c.1265T>A
NM_000162.3:c.1268T>A
NM_033507.1:c.1271T>A
NM_033508.1:c.1265T>A
NM_000162.4:c.1268T>A
NM_001354800.1:c.1268T>A
NM_001354801.1:c.257T>A
NM_001354802.1:c.128T>A
NM_001354803.1:c.302T>A
NM_033507.2:c.1271T>A
NM_033508.2:c.1265T>A
NM_033507.3:c.1271T>A
NM_033508.3:c.1265T>A

NM_001354803.2:c.302T>A

Pathogenic

Met criteria codes 6

PS4 PP2 PP3 PP4_Moderate PM2_Supporting PP1_Moderate

Not Met criteria codes 4

BA1 BS1 BP4 BP1

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.1268T>A variant in the glucokinase gene, GCK, causes an amino acid change of phenylalanine to tyrosine at codon 423 (p.(Phe423Tyr)) 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 0.801, 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 eight unrelated individuals with hyperglycemia (PS4; PMIDs: 23843579, 31968686, internal lab contributors). This variant segregated with hyperglycemia, with three informative meioses in two families (PP1_Moderate; PMIDs: 28012402, 23843579). 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 with minimal increment <3 mmol/l) (PP4_Moderate; PMID: 23843579). In summary, c.1268T>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): PS4, PP4_Moderate, PP1_Moderate, PM2_supporting, PP2, PP3.

Met criteria codes

PS4	✔	This variant was identified in eight unrelated individuals with hyperglycemia (PS4; PMIDs: 23843579, 31968686, 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 0.801, 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 with minimal increment <3 mmol/l) (PP4_Moderate; PMID: 23843579).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). absent from gnomAD v4.0.0
PP1_Moderate	✔	This variant segregated with hyperglycemia, with three informative meioses in two families (PP1_Moderate; PMIDs: 28012402, 23843579).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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