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.1136C>A (p.Ala379Glu)

Version: 1.0

CA213717

36177 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: c30cb401-f812-42f1-ba1f-37b5ab184ee6
Approved on: 2023/7/17
Published on: 2023/7/17

HGVS expressions

NM_000162.5:c.1136C>A
NM_000162.5(GCK):c.1136C>A (p.Ala379Glu)
NC_000007.14:g.44145614G>T
CM000669.2:g.44145614G>T
NC_000007.13:g.44185213G>T
CM000669.1:g.44185213G>T
NC_000007.12:g.44151738G>T
NG_008847.1:g.48810C>A
NG_008847.2:g.57557C>A
ENST00000395796.8:c.*1134C>A
ENST00000616242.5:c.*256C>A
ENST00000683378.1:n.362C>A
ENST00000336642.9:c.170C>A
ENST00000345378.7:c.1139C>A
ENST00000403799.8:c.1136C>A
ENST00000671824.1:c.1199C>A
ENST00000672743.1:n.148C>A
ENST00000673284.1:c.1136C>A
ENST00000336642.8:c.188C>A
ENST00000345378.6:c.1139C>A
ENST00000395796.7:c.1133C>A
ENST00000403799.7:c.1136C>A
ENST00000437084.1:c.1085C>A
ENST00000459642.1:n.516C>A
ENST00000616242.4:c.1133C>A
NM_000162.3:c.1136C>A
NM_033507.1:c.1139C>A
NM_033508.1:c.1133C>A
NM_000162.4:c.1136C>A
NM_001354800.1:c.1136C>A
NM_001354801.1:c.125C>A
NM_001354802.1:c.-5C>A
NM_001354803.1:c.170C>A
NM_033507.2:c.1139C>A
NM_033508.2:c.1133C>A
NM_033507.3:c.1139C>A
NM_033508.3:c.1133C>A

NM_001354803.2:c.170C>A

Likely Pathogenic

Met criteria codes 6

PM2_Supporting PS4_Moderate PM3 PP2 PP3 PP4

Not Met criteria codes 1

PS3

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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1136C>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to proline at codon 379 (p.(Ala379Glu)) of NM_000162.5. GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.985, 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 five unrelated individuals with non-autoimmune/insulin-deficient diabetes (PS4_Moderate; PMID 30592380, internal lab contributors). This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; PMID: 30592389) (PP4; internal lab contributors). This variant has been detected in one individual with neonatal diabetes. This individual was compound heterozygous for the variant and a pathogenic variant and was confirmed in trans by parental/family testing (PM3; PMID 30592380). Functional studies demonstrated the p.Ala379Glu protein has RAI<0.5; however, the wild-type kinetic parameters didn't pass the quality control, and the PS3 cannot be applied (PMID: 30592380). 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 1.2.0, approved 6/7/2023): PP2, PP3, PM2_Supporting, PP4, PM3, PS4_Moderate.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in five unrelated individuals with non-autoimmune/insulin-deficient diabetes (PS4_Moderate; PMID 30592380, internal lab contributors).
PM3	✔	This variant has been detected in an individual with neonatal diabetes. This individual was compound heterozygous for the variant and a pathogenic variant and was confirmed in trans by parental/family testing (PMID 30592380).
PP2	✔	GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.985, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).

PP4		✔	This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; PMID: 30592389).

Not Met criteria codes

PS3		✖	Functional studies demonstrated the p.Ala379Glu protein has RAI<0.5; however, the wild-type kinetic parameters didn’t pass the quality control, and PS3 cannot be applied (PMID: 30592380).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.