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
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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 PP2 PP3 PP4 PM3

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).
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).

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).

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