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.677T>C (p.Val226Ala)

Version: 1.0

CA213828

36244 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 06989f1f-d6e7-4ad1-ba67-9eba226362ca
Approved on: 2023/10/13
Published on: 2023/10/13

HGVS expressions

NM_000162.5:c.677T>C
NM_000162.5(GCK):c.677T>C (p.Val226Ala)
NC_000007.14:g.44149762A>G
CM000669.2:g.44149762A>G
NC_000007.13:g.44189361A>G
CM000669.1:g.44189361A>G
NC_000007.12:g.44155886A>G
NG_008847.1:g.44662T>C
NG_008847.2:g.53409T>C
ENST00000395796.8:c.*675T>C
ENST00000616242.5:c.677T>C
ENST00000682635.1:n.1163T>C
ENST00000345378.7:c.680T>C
ENST00000403799.8:c.677T>C
ENST00000671824.1:c.677T>C
ENST00000673284.1:c.677T>C
ENST00000345378.6:c.680T>C
ENST00000395796.7:c.674T>C
ENST00000403799.7:c.677T>C
ENST00000437084.1:c.626T>C
ENST00000616242.4:c.674T>C
NM_000162.3:c.677T>C
NM_033507.1:c.680T>C
NM_033508.1:c.674T>C
NM_000162.4:c.677T>C
NM_001354800.1:c.677T>C
NM_033507.2:c.680T>C
NM_033508.2:c.674T>C
NM_033507.3:c.680T>C
NM_033508.3:c.674T>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PM5_Supporting PM1 PP2 PP3

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.677T>C variant in the glucokinase gene, GCK, causes an amino acid change of valine to alanine at codon 226 (p.(Val226Ala)) of NM_000162.5. This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). 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 0.822, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Another missense variant, c.676G>A p.Val226Met, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Val226Ala (PM5_Supporting). In summary, c.677T>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PM1, PP2, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

PM2_Supporting ✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting ✔	Another missense variant, c.676G>A p.Val226Met, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Val226Ala (PM5_Supporting).
PM1 ✔	This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
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 0.822, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Curation History

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