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_001354803.2:c.146G>A

Version: 1.0

CA367398935

2578347 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b1d7557e-5fd6-45dd-86a1-c5c03cf413b9
Approved on: 2023/8/9
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HGVS expressions

NM_001354803.2:c.146G>A
NC_000007.14:g.44145638C>T
CM000669.2:g.44145638C>T
NC_000007.13:g.44185237C>T
CM000669.1:g.44185237C>T
NC_000007.12:g.44151762C>T
NG_008847.1:g.48786G>A
NG_008847.2:g.57533G>A
ENST00000395796.8:c.*1110G>A
ENST00000616242.5:c.*232G>A
ENST00000683378.1:n.338G>A
ENST00000336642.9:c.146G>A
ENST00000345378.7:c.1115G>A
ENST00000403799.8:c.1112G>A
ENST00000671824.1:c.1175G>A
ENST00000672743.1:n.124G>A
ENST00000673284.1:c.1112G>A
ENST00000336642.8:c.164G>A
ENST00000345378.6:c.1115G>A
ENST00000395796.7:c.1109G>A
ENST00000403799.7:c.1112G>A
ENST00000437084.1:c.1061G>A
ENST00000459642.1:n.492G>A
ENST00000616242.4:c.1109G>A
NM_000162.3:c.1112G>A
NM_033507.1:c.1115G>A
NM_033508.1:c.1109G>A
NM_000162.4:c.1112G>A
NM_001354800.1:c.1112G>A
NM_001354801.1:c.101G>A
NM_001354802.1:c.-29G>A
NM_001354803.1:c.146G>A
NM_033507.2:c.1115G>A
NM_033508.2:c.1109G>A
NM_000162.5:c.1112G>A
NM_033507.3:c.1115G>A
NM_033508.3:c.1109G>A

Likely Pathogenic

Met criteria codes 5

PP1_Strong PP2 PP3 PM2 PM5_Supporting

Not Met criteria codes 1

PP4

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.1112G>A variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to tyrosine at codon 371 (p.(Cys371Tyr)) 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 0.956, 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 segregated with diabetes with 5 informative meioses in a family with diabetes/hyperglycemia (PP1_Strong; internal lab contributors). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors). Another missense variant, c.1112G>T p.(Cys371Phe), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.(Cys371Tyr) (PM5_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for GENE-MODY. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2.0, approved 6/7/2023): PP2, PP3, PM2_Supporting, PP1_Strong, PM5_Supporting.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes with 5 informative meioses in a family with diabetes/hyperglycemia (PP1_Strong; 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 0.956, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.1112G>T p.(Cys371Phe) , has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.(Cys371Tyr)(PM5_Supporting).

Not Met criteria codes

PP4	✖	This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors).

Curation History

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