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.364C>A (p.Leu122Ile)

Version: 1.0

CA367402232

435307 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 411e8389-5fc7-42f7-93da-64160c730df4
Approved on: 2024/3/7
Published on: 2024/3/7

HGVS expressions

NM_000162.5:c.364C>A
NM_000162.5(GCK):c.364C>A (p.Leu122Ile)
NC_000007.14:g.44151075G>T
CM000669.2:g.44151075G>T
NC_000007.13:g.44190674G>T
CM000669.1:g.44190674G>T
NC_000007.12:g.44157199G>T
NG_008847.1:g.43349C>A
NG_008847.2:g.52096C>A
ENST00000395796.8:c.*362C>A
ENST00000616242.5:c.364C>A
ENST00000682635.1:n.850C>A
ENST00000345378.7:c.367C>A
ENST00000403799.8:c.364C>A
ENST00000671824.1:c.364C>A
ENST00000673284.1:c.364C>A
ENST00000345378.6:c.367C>A
ENST00000395796.7:c.361C>A
ENST00000403799.7:c.364C>A
ENST00000437084.1:c.364-51C>A
ENST00000616242.4:c.361C>A
NM_000162.3:c.364C>A
NM_033507.1:c.367C>A
NM_033508.1:c.361C>A
NM_000162.4:c.364C>A
NM_001354800.1:c.364C>A
NM_033507.2:c.367C>A
NM_033508.2:c.361C>A
NM_033507.3:c.367C>A
NM_033508.3:c.361C>A

Likely Pathogenic

Met criteria codes 5

PM2 PM5_Supporting PP2 PP3 PP4_Moderate

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.364C>A variant in the glucokinase gene, GCK, causes an amino acid change of leucine to isoleucine at codon 122 (p.(Leu122Ile)) 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 0.91, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). 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 antibody negative) (PP4_Moderate; internal lab contributors). Another missense variant, c.364C>T, p.Leu122Phe, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). Taken together, this evidence supports the classification of c.364C>A 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): PP4_Moderate, PM2_Supporting, PM5_Supporting, PP2, PP3.

Met criteria codes

PM2	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.0.0 Popmax filtering allele frequency due to one copy in the European non-Finnish subpopulation and no copies in any other subpopulation
PM5_Supporting	✔	Another missense variant, c.364C>T, p.Leu122Phe, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
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 0.91, 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 antibody negative) (PP4_Moderate; internal lab contributors).

Curation History

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