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Variant: NM_000162.5(GCK):c.364C>G (p.Leu122Val)

Version: 1.0

CA367402231

585919 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 25fc2a3a-7b48-4702-8b8e-3fa4032d8f9c
Approved on: 2024/3/11
Published on: 2024/3/11

HGVS expressions

NM_000162.5(GCK):c.364C>G (p.Leu122Val)
NM_000162.5:c.364C>G
NC_000007.14:g.44151075G>C
CM000669.2:g.44151075G>C
NC_000007.13:g.44190674G>C
CM000669.1:g.44190674G>C
NC_000007.12:g.44157199G>C
NG_008847.1:g.43349C>G
NG_008847.2:g.52096C>G
ENST00000395796.8:c.*362C>G
ENST00000616242.5:c.364C>G
ENST00000682635.1:n.850C>G
ENST00000345378.7:c.367C>G
ENST00000403799.8:c.364C>G
ENST00000671824.1:c.364C>G
ENST00000673284.1:c.364C>G
ENST00000345378.6:c.367C>G
ENST00000395796.7:c.361C>G
ENST00000403799.7:c.364C>G
ENST00000437084.1:c.364-51C>G
ENST00000616242.4:c.361C>G
NM_000162.3:c.364C>G
NM_033507.1:c.367C>G
NM_033508.1:c.361C>G
NM_000162.4:c.364C>G
NM_001354800.1:c.364C>G
NM_033507.2:c.367C>G
NM_033508.2:c.361C>G
NM_033507.3:c.367C>G
NM_033508.3:c.361C>G

Likely Pathogenic

Met criteria codes 6

PP1_Moderate | PM5_Supporting | PM2_Supporting | PP2 | PP3 | PP4

Not Met criteria codes 1

PS4

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>G variant in the glucokinase gene, GCK, causes an amino acid change of leucine to valine at codon 122 (p.(Leu122Val)) 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 0.948, 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 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs: 11508276, 32468610, internal lab contributors). Two of these individuals and one relative had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; PMID: 32468610, internal lab contributors). This variant segregated with hyperglycemia, with 3 informative meioses in 2 families (PP1; PMIDs: 32468610). 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>G 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): PP1_Moderate, PM5_Supporting, PM2_Supporting, PP2, PP3, PP4.

Met criteria codes

PP1_Moderate	✔	This variant segregated with hyperglycemia, with 3 informative meioses in 2 families (PP1; PMIDs: 32468610).
PM5_Supporting	✔	Another missense variant, c.364C>T, p.Leu122Phe, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.0.0, one copy in European (non-Finnish)
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 0.948, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4	✔	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%) (PP4; internal lab contributors).

Not Met criteria codes

PS4	✖	This variant was identified in 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs: 11508276, 32468610, internal lab contributors).

Curation History

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