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Variant: NM_000162.5(GCK):c.464G>C (p.Arg155Thr)

Version: 1.0

CA367401902

447401 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 67f52845-249a-4f84-ab2a-1dc4286da221
Approved on: 2024/4/19
Published on: 2024/4/19

HGVS expressions

NM_000162.5:c.464G>C
NM_000162.5(GCK):c.464G>C (p.Arg155Thr)
NC_000007.14:g.44150975C>G
CM000669.2:g.44150975C>G
NC_000007.13:g.44190574C>G
CM000669.1:g.44190574C>G
NC_000007.12:g.44157099C>G
NG_008847.1:g.43449G>C
NG_008847.2:g.52196G>C
ENST00000395796.8:c.*462G>C
ENST00000616242.5:c.464G>C
ENST00000682635.1:n.950G>C
ENST00000345378.7:c.467G>C
ENST00000403799.8:c.464G>C
ENST00000671824.1:c.464G>C
ENST00000673284.1:c.464G>C
ENST00000345378.6:c.467G>C
ENST00000395796.7:c.461G>C
ENST00000403799.7:c.464G>C
ENST00000437084.1:c.413G>C
ENST00000616242.4:c.461G>C
NM_000162.3:c.464G>C
NM_033507.1:c.467G>C
NM_033508.1:c.461G>C
NM_000162.4:c.464G>C
NM_001354800.1:c.464G>C
NM_033507.2:c.467G>C
NM_033508.2:c.461G>C
NM_033507.3:c.467G>C
NM_033508.3:c.461G>C

Likely Pathogenic

Met criteria codes 5

PP4_Moderate | PM5_Supporting | PP2 | PP3 | PM2_Supporting

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.464G>C variant in the glucokinase gene, GCK, causes an amino acid change of arginine to threonine at codon 155 (p.(Arg155Thr)) 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 0.814, 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.465G>T p.(Arg155Ser), has been classified as likely pathogenic by the ClinGen MDEP (PM5_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; PMID: 19410318). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID:19410318, ClinVar). In summary, c.464G>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): PM2_Supporting, PM5_Supporting, PP3, PP2, PP4_Moderate.

Met criteria codes

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; PMID: 19410318).
PM5_Supporting	✔	Another missense variant, c.465G>T p.(Arg155Ser), 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 0.814, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS4	✖	

This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID:19410318, ClinVar).

Curation History

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