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Variant: NM_000162.5(GCK):c.658T>C (p.Cys220Arg)

Version: 1.0

CA213820

36239 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: caf94c5b-c2a1-4625-a33e-27e9c0585d91
Approved on: 2023/12/1
Published on: 2023/12/1

HGVS expressions

NM_000162.5(GCK):c.658T>C (p.Cys220Arg)
NM_000162.5:c.658T>C
NC_000007.14:g.44149781A>G
CM000669.2:g.44149781A>G
NC_000007.13:g.44189380A>G
CM000669.1:g.44189380A>G
NC_000007.12:g.44155905A>G
NG_008847.1:g.44643T>C
NG_008847.2:g.53390T>C
ENST00000395796.8:c.*656T>C
ENST00000616242.5:c.658T>C
ENST00000682635.1:n.1144T>C
ENST00000345378.7:c.661T>C
ENST00000403799.8:c.658T>C
ENST00000671824.1:c.658T>C
ENST00000673284.1:c.658T>C
ENST00000345378.6:c.661T>C
ENST00000395796.7:c.655T>C
ENST00000403799.7:c.658T>C
ENST00000437084.1:c.607T>C
ENST00000616242.4:c.655T>C
NM_000162.3:c.658T>C
NM_033507.1:c.661T>C
NM_033508.1:c.655T>C
NM_000162.4:c.658T>C
NM_001354800.1:c.658T>C
NM_033507.2:c.661T>C
NM_033508.2:c.655T>C
NM_033507.3:c.661T>C
NM_033508.3:c.655T>C

Likely Pathogenic

Met criteria codes 5

PP4_Moderate | PP2 | PP3 | PM3_Supporting | 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.658T>C variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to arginine at codon 220 (p.(Cys220Arg)) of NM_000162.5. This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs: 4097065, 25755231, internal lab contributors). This variant was identified in in the homozygous state in 2 siblings with neonatal diabetes, negative testing for ABCC8, KCNJ11, and INS, and a 3+ generation family history of diabetes (PP4_Moderate, PM3_Supporting; PMID: 25755231, internal lab contributors). 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 0.8399, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, c.658T>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): PP4_Moderate, PP2, PP3, PM2_Supporting, PM3_Supporting.

Met criteria codes

PP4_Moderate	✔	This variant was identified in in the homozygous state in 2 siblings with neonatal diabetes, negative testing for ABCC8, KCNJ11, and INS, and a 3+ generation family history of diabetes (PP4_Moderate; PMID: 25755231, 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 0.8399, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM3_Supporting	✔	This variant has been detected in 2 siblings with neonatal diabetes in the homozygous state (PM3_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs: 4097065, 25755231, internal lab

contributors).

Curation History

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