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Variant: NM_033508.3:c.229G>C

Version: 1.0

CA367403045

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0e1ec57f-afe3-460d-b3a6-d839b66635d3
Approved on: 2024/12/2
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HGVS expressions

NM_033508.3:c.229G>C
NC_000007.14:g.44152402C>G
CM000669.2:g.44152402C>G
NC_000007.13:g.44192001C>G
CM000669.1:g.44192001C>G
NC_000007.12:g.44158526C>G
NG_008847.1:g.42022G>C
NG_008847.2:g.50769G>C
ENST00000395796.8:c.*230G>C
ENST00000616242.5:c.232G>C
ENST00000682635.1:n.718G>C
ENST00000345378.7:c.235G>C
ENST00000403799.8:c.232G>C
ENST00000671824.1:c.232G>C
ENST00000673284.1:c.232G>C
ENST00000345378.6:c.235G>C
ENST00000395796.7:c.229G>C
ENST00000403799.7:c.232G>C
ENST00000437084.1:c.232G>C
ENST00000616242.4:c.229G>C
NM_000162.3:c.232G>C
NM_033507.1:c.235G>C
NM_033508.1:c.229G>C
NM_000162.4:c.232G>C
NM_001354800.1:c.232G>C
NM_033507.2:c.235G>C
NM_033508.2:c.229G>C
NM_000162.5:c.232G>C
NM_033507.3:c.235G>C

Pathogenic

Met criteria codes 6

PM2_Supporting PP2 PP3 PM1 PP4_Moderate PP1_Strong

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS4

Evidence Links 0

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.232G>C variant in the glucokinase gene, GCK, causes an amino acid change of aspartic acid to histidine at codon 78 (p.(Asp78His)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 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 0.971, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Furthermore, this variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). 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 (PMID: 14517956, 28842611, 34440516). One of the individuals harboring this variant had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and a three generation family history) (PP4_Moderate; PMID: 34440516). Additonally, this variant segregated with hyperglycemia, with at least 5 informative meioses in a single family (PP1_Strong; PMID: 36257325, internal lab contributors). In summary, c.232G>C meets the criteria to be classified as 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, PP2, PP3, PM1, PP4_Moderate, PP1_Strong).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_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 0.971, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM1	✔	This variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and a three generation family history) (PP4_Moderate; PMID: 34440516).
PP1_Strong	✔	This variant segregated with hyperglycemia, with at least 5 informative meioses in a single family (PP1_Strong; PMID: 36257325, internal lab contributors).

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 (PMID: 14517956, 28842611, 34440516).

Curation History

Showing 1 to 1 of 1 rows

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