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

Version: 1.0

CA367403047

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: d4ccd1e7-1a69-4c30-8a29-443c2cc6e5ce
Approved on: 2024/12/2
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HGVS expressions

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

Pathogenic

Met criteria codes 6

PM1 PM5_Strong PP4_Moderate PP2 PP3 PM2_Supporting

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>A variant in the glucokinase gene, GCK, causes an amino acid change of aspartic acid to asparagine at codon 78 (p.(Asp78Asn)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 and v4.1 (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 0.947, 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: 36257325, internal lab contributors). 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 negative antiboides) (PP4_Moderate; internal lab contributors). Two other missense variants, c.234C>G (p.Asp78Glu) and c.232G>C (p.Asp78His) have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong). In summary, c.232G>A 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, PM5_Strong.

Met criteria codes

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).
PM5_Strong	✔	Two other missense variants, c.234C>G (p.Asp78Glu) and c.232G>C (p.Asp78His) have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong).
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 3 generation family history of hyperglycemia) (PP4_Moderate; 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 0.947, 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). Absent from gnomAD v4.1

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: 36257325, internal lab contributors).

Curation History

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