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Variant: NM_033508.3:c.680C>A

Version: 1.0

CA367400788

3024421 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5e3e9831-18b4-43bd-a2f0-8edec94b1ab8
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HGVS expressions

NM_033508.3:c.680C>A
NC_000007.14:g.44147830G>T
CM000669.2:g.44147830G>T
NC_000007.13:g.44187429G>T
CM000669.1:g.44187429G>T
NC_000007.12:g.44153954G>T
NG_008847.1:g.46594C>A
NG_008847.2:g.55341C>A
ENST00000395796.8:c.*681C>A
ENST00000616242.5:c.683C>A
ENST00000345378.7:c.686C>A
ENST00000403799.8:c.683C>A
ENST00000671824.1:c.683C>A
ENST00000673284.1:c.683C>A
ENST00000345378.6:c.686C>A
ENST00000395796.7:c.680C>A
ENST00000403799.7:c.683C>A
ENST00000437084.1:c.632C>A
ENST00000616242.4:c.680C>A
NM_000162.3:c.683C>A
NM_033507.1:c.686C>A
NM_033508.1:c.680C>A
NM_000162.4:c.683C>A
NM_001354800.1:c.683C>A
NM_033507.2:c.686C>A
NM_033508.2:c.680C>A
NM_000162.5:c.683C>A
NM_033507.3:c.686C>A

Pathogenic

Met criteria codes 6

PP2 PP3 PM1 PM5_Strong PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PS4

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

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.683C>A variant in the glucokinase gene, GCK, causes an amino acid change of threonine to lysine at codon 228 (p.(Thr228Lys)) 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 0.976, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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 is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 2 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 19790256, internal lab contributor). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (persistent FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributor). Two other missense variants, c.683C>T p.Thr228Met and c.682A>G p.Thr228Ala, have been classified as pathogenic by the ClinGen MDEP (PM5_Strong). In summary, c.683C>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, approved 8/11/2023): PM1, PP2, PP3, PM2_Supporting, PM5_Strong, PP4_Moderate.

Met criteria codes

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 0.976, 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).
PM5_Strong	✔	Two other missense variants, c.683C>T p.Thr228Met and c.682A>G p.Thr228Ala, have been classified 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 (persistent FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies)(PP4_Moderate; internal lab contributor).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in 2 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 19790256, internal lab contributor).

Curation History

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