Variant: NM_033508.3:c.817G>A

Version: 1.1

CA367400488

3383924 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 1ee3be95-bcae-4658-a78b-6562fe0e8e21
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HGVS expressions

NM_033508.3:c.817G>A
NC_000007.14:g.44147693C>T
CM000669.2:g.44147693C>T
NC_000007.13:g.44187292C>T
CM000669.1:g.44187292C>T
NC_000007.12:g.44153817C>T
NG_008847.1:g.46731G>A
NG_008847.2:g.55478G>A
ENST00000395796.8:c.*818G>A
ENST00000616242.5:c.820G>A
ENST00000345378.7:c.823G>A
ENST00000403799.8:c.820G>A
ENST00000671824.1:c.820G>A
ENST00000673284.1:c.820G>A
ENST00000345378.6:c.823G>A
ENST00000395796.7:c.817G>A
ENST00000403799.7:c.820G>A
ENST00000437084.1:c.769G>A
ENST00000616242.4:c.817G>A
NM_000162.3:c.820G>A
NM_033507.1:c.823G>A
NM_033508.1:c.817G>A
NM_000162.4:c.820G>A
NM_001354800.1:c.820G>A
NM_033507.2:c.823G>A
NM_033508.2:c.817G>A
NM_000162.5:c.820G>A
NM_033507.3:c.823G>A

Likely Pathogenic

Met criteria codes 7

PP1 PP2 PP3 PM5_Supporting PM2_Supporting PP4_Moderate PS4_Moderate

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.820G>A variant in the glucokinase gene, GCK, is a missense variant resulting in an amino acid change of aspartic acid to asparagine at codon 274 (p.(Asp274Asn)) 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). Additionally, it is predicted to be deleterious by computational evidence, with a REVEL score of 0.935, which is greater than the MDEP VCEP threshold of 0.70 (PP3). 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 negative antibodies) (PP4_Moderate; internal lab contributor). Furthermore, the variant segregated with diabetes in this family with three informative meioses (PP1, internal lab contributors). This variant was identified in four unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMIDs: 32086287, 36257325, internal lab contributors). Another missense variant at the same amino acid, c.820G>A p.(Asp274Ala), has been classified as pathogenic by the ClinGen MDEP, but p.Asp274Asn has a smaller Grantham distance (PM5_Supporting). In summary, c.820G>A variant meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PS4_Moderate; PM2_Supporting, PP2, PP3, PP4_Moderate, PP1, PM5_Supporting.

Met criteria codes

PP1	✔	This variant segregated with diabetes in a single family with 3 informative meioses (PP1, internal lab contributor).
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 0.935, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5_Supporting	✔	Another missense variant at the same amino acid, c.820G>A p.(Asp274Ala), has been classified as pathogenic by the ClinGen MDEP, but and p.Asp274Asn has a smaller Grantham distance (PM5_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
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 negative antibodies) (PP4_Moderate; internal lab contributor).
PS4_Moderate	✔	This variant was identified in four unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PP4_Moderate; PMIDs: 32086287, 36257325, internal lab contributors).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_033508.3:c.817G>A	Likely Pathogenic	Monogenic Diabetes	2025-10-28	1.1	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0	GCK
View	NM_033508.3:c.817G>A	Likely Pathogenic	Monogenic Diabetes	2024-11-05	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0	GCK

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