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Variant: NM_001354803.2:c.208C>A

Version: 2.0

CA367398628

2581305 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 9aafc77f-1c7a-4e68-8657-248772693e8d
Approved on: 2025/11/26
Published on: 2025/11/26

HGVS expressions

NM_001354803.2:c.208C>A
NC_000007.14:g.44145576G>T
CM000669.2:g.44145576G>T
NC_000007.13:g.44185175G>T
CM000669.1:g.44185175G>T
NC_000007.12:g.44151700G>T
NG_008847.1:g.48848C>A
NG_008847.2:g.57595C>A
ENST00000395796.8:c.*1172C>A
ENST00000616242.5:c.*294C>A
ENST00000683378.1:n.400C>A
ENST00000336642.9:c.208C>A
ENST00000345378.7:c.1177C>A
ENST00000403799.8:c.1174C>A
ENST00000671824.1:c.1237C>A
ENST00000672743.1:n.186C>A
ENST00000673284.1:c.1174C>A
ENST00000336642.8:c.226C>A
ENST00000345378.6:c.1177C>A
ENST00000395796.7:c.1171C>A
ENST00000403799.7:c.1174C>A
ENST00000437084.1:c.1123C>A
ENST00000459642.1:n.554C>A
ENST00000616242.4:c.1171C>A
NM_000162.3:c.1174C>A
NM_033507.1:c.1177C>A
NM_033508.1:c.1171C>A
NM_000162.4:c.1174C>A
NM_001354800.1:c.1174C>A
NM_001354801.1:c.163C>A
NM_001354802.1:c.34C>A
NM_001354803.1:c.208C>A
NM_033507.2:c.1177C>A
NM_033508.2:c.1171C>A
NM_000162.5:c.1174C>A
NM_033507.3:c.1177C>A
NM_033508.3:c.1171C>A

Pathogenic

Met criteria codes 7

PM5_Strong | PM2_Supporting | PP4_Moderate | PS3_Supporting | PP1 | PP2 | PP3

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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1174C>A variant in the glucokinase gene, GCK, causes an amino acid change of arginine to serine at codon 392 (p.(Arg392Ser)) 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 0.778, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 18382660, internal lab contributors). One of these individuals did have a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative) (PP4_Moderate; PMID: 18382660). This variant segregated with hyperglycemia, with two informative meioses in two families (PP1; PMID: 18382660, internal lab contributors). While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the relative stability index was below the MDEP cutoff of 0.5 (PS3_Supporting; PMID: 22761713). Two other missense variants at the same amino acid position, c.1174C>T p.(Arg392Cys) and c.1175G>T p.(Arg392Leu), have been classified as pathogenic by the ClinGen MDEP (PM5_Strong). In summary, c.1174C>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0 approved 10/10/2025): PP4_Moderate, PP2, PP3, PM2_Supporting, PM5_Strong, PS3_Supporting, PP1.

Met criteria codes

PM5_Strong	✔	Two other missense variants at the same amino acid position, c.1174C>T p.(Arg392Cys) and c.1175G>T p.(Arg392Leu), have been classified as pathogenic by the ClinGen MDEP (PM5_Strong).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (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 antibody negative) (PP4_Moderate; PMID: 18382660).
PS3_Supporting	✔	While the relative activity index (RAI) of this variant was above the MDEP cutoff of 0.5, the relative stability index was below the MDEP cutoff of 0.5 (PS3_Supporting; PMID: 22761713).
PP1	✔	This variant segregated with hyperglycemia, with two informative meioses in two families (PP1; PMID: 18382660, 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 0.778, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

PS4	✖	This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 18382660, internal lab contributors).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001354803.2:c.208C>A	Pathogenic	Monogenic Diabetes	2025-11-26	2.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 3.1.0	GCK
View	NM_001354803.2:c.208C>A	Likely Pathogenic	Monogenic Diabetes	2023-11-23	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0	GCK

Showing 1 to 2 of 2 rows

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