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Variant: NM_000162.5(GCK):c.608T>C (p.Val203Ala)

Version: 1.0

CA367401366

585923 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7305dd73-b842-458c-b7f8-5d8dd9f9cd7a
Approved on: 2023/7/31
Published on: 2023/7/31

HGVS expressions

NM_000162.5:c.608T>C
NM_000162.5(GCK):c.608T>C (p.Val203Ala)
NC_000007.14:g.44149831A>G
CM000669.2:g.44149831A>G
NC_000007.13:g.44189430A>G
CM000669.1:g.44189430A>G
NC_000007.12:g.44155955A>G
NG_008847.1:g.44593T>C
NG_008847.2:g.53340T>C
ENST00000395796.8:c.*606T>C
ENST00000616242.5:c.608T>C
ENST00000682635.1:n.1094T>C
ENST00000345378.7:c.611T>C
ENST00000403799.8:c.608T>C
ENST00000671824.1:c.608T>C
ENST00000673284.1:c.608T>C
ENST00000345378.6:c.611T>C
ENST00000395796.7:c.605T>C
ENST00000403799.7:c.608T>C
ENST00000437084.1:c.557T>C
ENST00000616242.4:c.605T>C
NM_000162.3:c.608T>C
NM_033507.1:c.611T>C
NM_033508.1:c.605T>C
NM_000162.4:c.608T>C
NM_001354800.1:c.608T>C
NM_033507.2:c.611T>C
NM_033508.2:c.605T>C
NM_033507.3:c.611T>C
NM_033508.3:c.605T>C

Pathogenic

Met criteria codes 7

PP2 PP3 PP1_Strong PS3_Moderate PS4 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PM1

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 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.608T>C variant in the glucokinase gene, GCK, causes an amino acid change of valine to alanine at codon 203 (p.(Val203Ala)) 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 absent from gnomAD v2.1.1 (PM2_Supporting), and has been identified in at least 15 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; ClinVar ID: 585923, PMIDs: 9075802, 9000695, 8433729, 15841481,19790256). At least one of these individuals has a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6-7.6%, antibody negative, and three-generation dominant family history of diabetes or hyperglycemia) (PP4_Moderate; PMID 15841481). This variant segregated with diabetes, with at least six informative meioses in five families with MODY (PP1_Strong; PMID:9075802, PMID:16059790). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.946, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Additionally, functional studies have determined that the c.608C>T variant has decreased catalytic activity as measured by a relative activity index (RAI) < 0.5 (PS3_Moderate; https://doi.org/10.1159/000079009). In summary, c.608C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.1, approved 3/23/2023): PP1_Strong, PS4, PP4_Moderate, PS3_Moderate, PP2, PP3, PM2_Supporting).

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 0.946, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong	✔	This variant segregated with diabetes, with at least six informative meioses in five families with MODY (PP1_Strong; PMIDs: 9075802, 16059790).
PS3_Moderate	✔	Functional studies in which quality control metrics were met have determined that the c.608C>T variant has decreased catalytic activity as measured by a relative activity index less than 0.5 (PS3_Moderate; https://doi.org/10.1159/000079009).
PS4	✔	This variant was identified in at least 15 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; ClinVar ID: 585923, PMID: 9075802, PMID:9000695, PMID: 8433729, PMID:15841481, PMID: 19790256).

PP4_Moderate		✔	This variant was identified in at least one individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%, antibody negative, and three-generation, dominant family history of diabetes or hyperglycemia) (PP4_Moderate; PMID 15841481). Toaima et al 2005 - family 4, patient diagnosed at 11yo, antibody negative, BMI 19.3, FBG 6.3, OGTT 10.0, C-pep 0.46, HbA1c 6.2%, treated with diet. History in her father and PGF.
PM2_Supporting		✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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