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Variant: NM_000162.5(GCK):c.605T>C (p.Met202Thr)

Version: 1.0

CA213810

36233 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0d897a5d-9b10-4f8b-8c76-5fb7e538d5b0
Approved on: 2023/12/1
Published on: 2023/12/1

HGVS expressions

NM_000162.5(GCK):c.605T>C (p.Met202Thr)
NM_000162.5:c.605T>C
NC_000007.14:g.44149834A>G
CM000669.2:g.44149834A>G
NC_000007.13:g.44189433A>G
CM000669.1:g.44189433A>G
NC_000007.12:g.44155958A>G
NG_008847.1:g.44590T>C
NG_008847.2:g.53337T>C
ENST00000395796.8:c.*603T>C
ENST00000616242.5:c.605T>C
ENST00000682635.1:n.1091T>C
ENST00000345378.7:c.608T>C
ENST00000403799.8:c.605T>C
ENST00000671824.1:c.605T>C
ENST00000673284.1:c.605T>C
ENST00000345378.6:c.608T>C
ENST00000395796.7:c.602T>C
ENST00000403799.7:c.605T>C
ENST00000437084.1:c.554T>C
ENST00000616242.4:c.602T>C
NM_000162.3:c.605T>C
NM_033507.1:c.608T>C
NM_033508.1:c.602T>C
NM_000162.4:c.605T>C
NM_001354800.1:c.605T>C
NM_033507.2:c.608T>C
NM_033508.2:c.602T>C
NM_033507.3:c.608T>C
NM_033508.3:c.602T>C

Pathogenic

Met criteria codes 6

PP2 PP3 PP1_Strong 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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.605C>T variant in the glucokinase gene, GCK, causes an amino acid change of methionine to threonine at codon 202 (p.(Met202Thr)) of NM_000162.5. This variant segregated with diabetes/hyperglycemia, with 6 informative meioses in 4 families (PP1_Strong; internal lab contributors). This variant was identified in 12 unrelated individuals with hyperglycemia (PS4; PMID: 17573000, internal lab contributors). This variant was identified in two individuals 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 contributors). 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 0.917, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has a gnomAD v2.1.1 Popmax filtering allele frequency of 0.000002920 (below the MDEP threshold of 0.000003) and 2 copies observed in the European non-Finnish population and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting). In summary, c.605C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_Strong, PS4, PP4_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 0.917, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia, with 6 informative meioses in 4 families (PP1_Strong; internal lab contributors).
PS4	✔	This variant was identified in 12 unrelated individuals with hyperglycemia (PS4; PMID: 17573000, internal lab contributors).
PP4_Moderate	✔	This variant was identified in two individuals 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 contributors).
PM2_Supporting	✔	This variant has a gnomAD v2.1.1 Popmax filtering allele frequency of 0.000002920 (below the MDEP threshold of 0.000003) and 2 copies observed in the European non-Finnish population and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting).

Not Met criteria codes

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

Curation History

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