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Variant: NM_033508.3:c.107T>C

Version: 1.0

CA367403544

2682651 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 3d99d62c-0311-40e5-a6bc-20262825de81
Approved on: 2023/12/8
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HGVS expressions

NM_033508.3:c.107T>C
NC_000007.14:g.44153399A>G
CM000669.2:g.44153399A>G
NC_000007.13:g.44192998A>G
CM000669.1:g.44192998A>G
NC_000007.12:g.44159523A>G
NG_008847.1:g.41025T>C
NG_008847.2:g.49772T>C
ENST00000395796.8:c.*108T>C
ENST00000616242.5:c.110T>C
ENST00000682635.1:n.596T>C
ENST00000345378.7:c.113T>C
ENST00000403799.8:c.110T>C
ENST00000671824.1:c.110T>C
ENST00000673284.1:c.110T>C
ENST00000345378.6:c.113T>C
ENST00000395796.7:c.107T>C
ENST00000403799.7:c.110T>C
ENST00000437084.1:c.110T>C
ENST00000476008.1:n.545T>C
ENST00000616242.4:c.107T>C
NM_000162.3:c.110T>C
NM_033507.1:c.113T>C
NM_033508.1:c.107T>C
NM_000162.4:c.110T>C
NM_001354800.1:c.110T>C
NM_033507.2:c.113T>C
NM_033508.2:c.107T>C
NM_000162.5:c.110T>C
NM_033507.3:c.113T>C

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PM5_Supporting PP2 PP3 PM2_Supporting

Not Met criteria codes 2

PS4 PP1

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.110T>C variant in the glucokinase gene, GCK, causes an amino acid change of methionine to threonine at codon 37 (p.(Met37Thr)) of NM_000162.5. This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%, and persistent impaired fasting glucose) (PP4_Moderate; PMID 28170077). 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 0.9559, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). Another missense variant, c.110T>C (p.Met37Arg), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Met37Thr (PM5_Supporting). This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDS: 33477506, 28170077, internal lab contributors). This variant segregated with diabetes with one informative meiosis in a family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 28170077). In summary, c.110T>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0 approved 8/11/2023): PP4_Moderate, PP2, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%, and persistent impaired fasting glucose) (PP4_Moderate; PMID 28170077).
PM5_Supporting	✔	Another missense variant, c.110T>C (p.Met37Arg), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Met37Thr (PM5_Supporting).
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 0.9559, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS4		✖	This variant was identified in three unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDS: 33477506, 28170077, internal lab contributors).
PP1		✖	This variant segregated with diabetes with one informative meiosis in a family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 28170077).

Curation History

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