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Variant: NM_033508.3:c.564C>G

Version: 1.0

CA367401545

2664364 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 26df7686-6891-4bb7-b8ce-dc169d2077c0
Approved on: 2023/12/2
Published on: 2023/12/2

HGVS expressions

NM_033508.3:c.564C>G
NC_000007.14:g.44149981G>C
CM000669.2:g.44149981G>C
NC_000007.13:g.44189580G>C
CM000669.1:g.44189580G>C
NC_000007.12:g.44156105G>C
NG_008847.1:g.44443C>G
NG_008847.2:g.53190C>G
ENST00000395796.8:c.*565C>G
ENST00000616242.5:c.567C>G
ENST00000682635.1:n.1053C>G
ENST00000345378.7:c.570C>G
ENST00000403799.8:c.567C>G
ENST00000671824.1:c.567C>G
ENST00000673284.1:c.567C>G
ENST00000345378.6:c.570C>G
ENST00000395796.7:c.564C>G
ENST00000403799.7:c.567C>G
ENST00000437084.1:c.516C>G
ENST00000616242.4:c.564C>G
NM_000162.3:c.567C>G
NM_033507.1:c.570C>G
NM_033508.1:c.564C>G
NM_000162.4:c.567C>G
NM_001354800.1:c.567C>G
NM_033507.2:c.570C>G
NM_033508.2:c.564C>G
NM_000162.5:c.567C>G
NM_033507.3:c.570C>G

Likely Pathogenic

Met criteria codes 6

PS2_Moderate PM5_Supporting PM2_Supporting PP2 PP3 PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Not Met criteria codes 2

PM1 PS4

Evidence Links 0

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.567C>G variant in the glucokinase gene, GCK, causes an amino acid change of isoleucine to methionine, at codon 189 (p.(Ile189Met)) of NM_000162.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Additionally, 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). Another missense variant, c.566T>C, p.Ile189Thr, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ile189Met (PM5_Supporting). Additionally, this variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.841, which is greater than the MDEP threshold of 0.70 (PP3). 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 contributors). This occurred in this individual as a de novo occurrence with unconfirmed parental relationships (PS2_Moderate; internal lab contributor). While this variant was identified in the individual mentioned above, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributor). In summary, this variant meets the criteria to be classified as likely pathogenic for monogenic diabetes. AMCG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PP4_Moderate, PM2_Supporting, PM5_Supporting, PP2, PP3, PS2_Moderate.

Met criteria codes

PS2_Moderate	✔	This variant was identified as a de novo occurrence with unconfirmed parental relationships in an individual with a clinical picture highly specific for GCK-hyperglycemia (PS2_Moderate; internal lab contributor).
PM5_Supporting	✔	Another missense variant, c.566T>C, p.Ile189Thr, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ile189Met.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_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 0.841, which is greater than the MDEP threshold of 0.70 (PP3).
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 contributors).

Not Met criteria codes

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

PS4		✖	This variant was identified in one individual who does not have autoimmune or absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributor).

Curation History

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