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Variant: NM_001354803.2:c.191T>G

Version: 1.0

CA367398699

3233999 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 2992b28b-4b89-44a2-9d65-21816c260221
Approved on: 2024/4/28
Published on: 2024/4/28

HGVS expressions

NM_001354803.2:c.191T>G
NC_000007.14:g.44145593A>C
CM000669.2:g.44145593A>C
NC_000007.13:g.44185192A>C
CM000669.1:g.44185192A>C
NC_000007.12:g.44151717A>C
NG_008847.1:g.48831T>G
NG_008847.2:g.57578T>G
ENST00000395796.8:c.*1155T>G
ENST00000616242.5:c.*277T>G
ENST00000683378.1:n.383T>G
ENST00000336642.9:c.191T>G
ENST00000345378.7:c.1160T>G
ENST00000403799.8:c.1157T>G
ENST00000671824.1:c.1220T>G
ENST00000672743.1:n.169T>G
ENST00000673284.1:c.1157T>G
ENST00000336642.8:c.209T>G
ENST00000345378.6:c.1160T>G
ENST00000395796.7:c.1154T>G
ENST00000403799.7:c.1157T>G
ENST00000437084.1:c.1106T>G
ENST00000459642.1:n.537T>G
ENST00000616242.4:c.1154T>G
NM_000162.3:c.1157T>G
NM_033507.1:c.1160T>G
NM_033508.1:c.1154T>G
NM_000162.4:c.1157T>G
NM_001354800.1:c.1157T>G
NM_001354801.1:c.146T>G
NM_001354802.1:c.17T>G
NM_001354803.1:c.191T>G
NM_033507.2:c.1160T>G
NM_033508.2:c.1154T>G
NM_000162.5:c.1157T>G
NM_033507.3:c.1160T>G
NM_033508.3:c.1154T>G

Likely Pathogenic

Met criteria codes 4

PM5_Strong | PM2_Supporting | 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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c. variant in the glucokinase gene, GCK, causes an amino acid change of leucine to arginine at codon 386 (p.(Leu386Arg)) 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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). Two other missense variants, c.1156C>G p.Leu386Val and c.1157T>C p.Leu386Pro, have been interpreted as pathogenic by the ClinGen MDEP, and p.Leu386Arg has a greater Grantham distance than p.Leu386Val and p.Leu386Pro (PM5_Strong). In summary, c.1157T>G 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): PM5_Strong, PP2, PP3, PM2_Supporting.

Met criteria codes

PM5_Strong	✔	Two other missense variants, c.1156C>G p.Leu386Val and c.1157T>C p.Leu386Pro, have been interpreted as pathogenic by the ClinGen MDEP, and p.Leu386Arg has a greater Grantham distance than p.Leu386Val and p.Leu386Pro (PM5_Strong). Leu-Val 32 Leu-Arg 102 Leu-Pro 98
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 0.979, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

PS4	✖	This variant was identified in 3 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).

Curation History

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