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Variant: NM_033508.3:c.386T>A

Version: 1.0

CA367402147

3024422 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 436c7bf1-e92f-4ab8-920a-396fde34039d
Approved on: 2024/2/28
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HGVS expressions

NM_033508.3:c.386T>A
NC_000007.14:g.44151050A>T
CM000669.2:g.44151050A>T
NC_000007.13:g.44190649A>T
CM000669.1:g.44190649A>T
NC_000007.12:g.44157174A>T
NG_008847.1:g.43374T>A
NG_008847.2:g.52121T>A
ENST00000395796.8:c.*387T>A
ENST00000616242.5:c.389T>A
ENST00000682635.1:n.875T>A
ENST00000345378.7:c.392T>A
ENST00000403799.8:c.389T>A
ENST00000671824.1:c.389T>A
ENST00000673284.1:c.389T>A
ENST00000345378.6:c.392T>A
ENST00000395796.7:c.386T>A
ENST00000403799.7:c.389T>A
ENST00000437084.1:c.364-26T>A
ENST00000616242.4:c.386T>A
NM_000162.3:c.389T>A
NM_033507.1:c.392T>A
NM_033508.1:c.386T>A
NM_000162.4:c.389T>A
NM_001354800.1:c.389T>A
NM_033507.2:c.392T>A
NM_033508.2:c.386T>A
NM_000162.5:c.389T>A
NM_033507.3:c.392T>A

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP1_Strong PM2_Supporting PM5_Supporting

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

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.389T>A variant in the glucokinase gene, GCK, causes an amino acid change of isoleucine to asparagine at codon 130 (p.(Ile130Asn)) 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 0.937, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 2 unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). This variant segregated with hyperglycemia, with 4 informative meioses in 2 families (PP1_Strong; internal lab contributors). Another missense variant, c.389T>C p.Ile130Thr, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). In summary, c.389T>A 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, approved 8/11/2023): PP2, PP3, PM2_Supporting, PM5_Supporting, PP1_Strong.

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 0.937, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong	✔	This variant segregated with hyperglycemia, with 4 informative meioses in 2 families (PP1_Strong; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.389T>C p.Ile389Thr, has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in 2 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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