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Variant: NM_000162.5(GCK):c.1229G>A (p.Gly410Asp)

Version: 2.1

CA367398309

447386 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: d064c5c8-3236-4805-ad04-ceb6948d456d
Approved on: 2024/6/22
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HGVS expressions

NM_000162.5(GCK):c.1229G>A (p.Gly410Asp)
NM_000162.5:c.1229G>A
NC_000007.14:g.44145521C>T
CM000669.2:g.44145521C>T
NC_000007.13:g.44185120C>T
CM000669.1:g.44185120C>T
NC_000007.12:g.44151645C>T
NG_008847.1:g.48903G>A
NG_008847.2:g.57650G>A
ENST00000395796.8:c.*1227G>A
ENST00000616242.5:c.*349G>A
ENST00000683378.1:n.455G>A
ENST00000336642.9:c.263G>A
ENST00000345378.7:c.1232G>A
ENST00000403799.8:c.1229G>A
ENST00000671824.1:c.1292G>A
ENST00000672743.1:n.241G>A
ENST00000673284.1:c.1229G>A
ENST00000336642.8:c.281G>A
ENST00000345378.6:c.1232G>A
ENST00000395796.7:c.1226G>A
ENST00000403799.7:c.1229G>A
ENST00000437084.1:c.1178G>A
ENST00000459642.1:n.609G>A
ENST00000616242.4:c.1226G>A
NM_000162.3:c.1229G>A
NM_033507.1:c.1232G>A
NM_033508.1:c.1226G>A
NM_000162.4:c.1229G>A
NM_001354800.1:c.1229G>A
NM_001354801.1:c.218G>A
NM_001354802.1:c.89G>A
NM_001354803.1:c.263G>A
NM_033507.2:c.1232G>A
NM_033508.2:c.1226G>A
NM_033507.3:c.1232G>A
NM_033508.3:c.1226G>A

NM_001354803.2:c.263G>A

Pathogenic

Met criteria codes 7

PP4_Moderate PM2_Supporting PM1 PM5 PP1 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.1229G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to aspartate at codon 410 (p.(Gly410Asp)) 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 resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.991, 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 segregated with hyperglycemia, with 2 informative meioses in 2 families (PP1; internal lab contributors). 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 antibody negative) (PP4_Moderate; internal lab contributors). 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 (internal lab contributors). Another missense variant, c.1228G>A p.Gly410Ser, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gly410Asp has a greater Grantham distance (PM5). In summary, c.1229G>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 1.3.0, approved 8/11/2023): PM1, PP2, PP3, PM2_Supporting, PM5, PP1, PP4_moderate.

Met criteria codes

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 antibody negative) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 0 copies in gnomAD v4.1.0
PM1	✔	This variant resides in an amino acid that directly binds ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
PM5	✔	Another missense variant, c.1228G>A p.Gly410Ser, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gly410Asp has a greater Grantham distance (PM5).
PP1	✔	This variant segregated with hyperglycemia, with 2 informative meioses in two families (PP1; internal lab contributors).

PP2	ℹ	✔	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	ℹ	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.991, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

PS4	ℹ	✖	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 (internal lab contributors).

Curation History

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