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Variant: NM_000162.5(GCK):c.1240A>G (p.Lys414Glu)

Version: 1.0

CA213739

36188 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 887ffb3c-717c-4c08-8aa1-5319b0be7b76
Approved on: 2023/6/26
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HGVS expressions

NM_000162.5(GCK):c.1240A>G (p.Lys414Glu)
NM_000162.5:c.1240A>G
NC_000007.14:g.44145510T>C
CM000669.2:g.44145510T>C
NC_000007.13:g.44185109T>C
CM000669.1:g.44185109T>C
NC_000007.12:g.44151634T>C
NG_008847.1:g.48914A>G
NG_008847.2:g.57661A>G
ENST00000395796.8:c.*1238A>G
ENST00000616242.5:c.*360A>G
ENST00000683378.1:n.466A>G
ENST00000336642.9:c.274A>G
ENST00000345378.7:c.1243A>G
ENST00000403799.8:c.1240A>G
ENST00000671824.1:c.1303A>G
ENST00000672743.1:n.252A>G
ENST00000673284.1:c.1240A>G
ENST00000336642.8:c.292A>G
ENST00000345378.6:c.1243A>G
ENST00000395796.7:c.1237A>G
ENST00000403799.7:c.1240A>G
ENST00000437084.1:c.1189A>G
ENST00000459642.1:n.620A>G
ENST00000616242.4:c.1237A>G
NM_000162.3:c.1240A>G
NM_033507.1:c.1243A>G
NM_033508.1:c.1237A>G
NM_000162.4:c.1240A>G
NM_001354800.1:c.1240A>G
NM_001354801.1:c.229A>G
NM_001354802.1:c.100A>G
NM_001354803.1:c.274A>G
NM_033507.2:c.1243A>G
NM_033508.2:c.1237A>G
NM_033507.3:c.1243A>G
NM_033508.3:c.1237A>G

NM_001354803.2:c.274A>G

Pathogenic

Met criteria codes 7

PM1 PP1_Strong PS4 PM2_Supporting PP2 PP3 PP4

Not Met criteria codes 1

PS3

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.1240A>G variant in the glucokinase gene, GCK, causes an amino acid change of lysine to glutamic acid at codon 414 (p.(Lys414Glu)) 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), and is predicted to be deleterious by computational evidence, with a REVEL score of 0.9279, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 (PM2_Supporting), and was identified in seven unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; ClinVar ID 36188, PMID 18411240, internal lab contributors). The variant segregated with diabetes, with 5 informative meioses in three families with MODY (PP1_Strong; internal lab contributors). Additionally, one of these individuals has a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributor). In summary, c.1240A>G meets the criteria to be classified as pathogenic by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PP1_Strong, PS4, PP4, PM1, PP2, PP3, PM2_Supporting.

Met criteria codes

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)
PP1_Strong	✔	This variant segregated with diabetes, with 5 informative meioses in three families with MODY (PP1_Strong; internal lab contributors).
PS4	✔	This variant was identified in seven unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; ClinVar ID 36188, PMID 18411240, internal lab contributors).
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 0.9279, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

PP4 ✔ 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%) (PP4; internal lab contributor).

Not Met criteria codes

PS3 ✖ While studies exploring the effect of this variant on protein function have been performed, these studies do not meet the criteria set forth by the MDEP for the application of PS3 or BS3 (PMID: 17353190, PMID: 21831042, PMID: 7619052, PMID: 8325892, PMID: 10525657).

Curation History

Showing 1 to 1 of 1 rows

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