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Variant: NM_000162.5(GCK):c.214G>A (p.Gly72Arg)

Version: 1.0

CA213771

36209 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: f7b1c7c0-e94c-4adc-9ff1-69192f1f5cd3
Approved on: 2023/8/13
Published on: 2023/8/13

HGVS expressions

NM_000162.5:c.214G>A
NM_000162.5(GCK):c.214G>A (p.Gly72Arg)
NC_000007.14:g.44152420C>T
CM000669.2:g.44152420C>T
NC_000007.13:g.44192019C>T
CM000669.1:g.44192019C>T
NC_000007.12:g.44158544C>T
NG_008847.1:g.42004G>A
NG_008847.2:g.50751G>A
ENST00000395796.8:c.*212G>A
ENST00000616242.5:c.214G>A
ENST00000682635.1:n.700G>A
ENST00000345378.7:c.217G>A
ENST00000403799.8:c.214G>A
ENST00000671824.1:c.214G>A
ENST00000673284.1:c.214G>A
ENST00000345378.6:c.217G>A
ENST00000395796.7:c.211G>A
ENST00000403799.7:c.214G>A
ENST00000437084.1:c.214G>A
ENST00000616242.4:c.211G>A
NM_000162.3:c.214G>A
NM_033507.1:c.217G>A
NM_033508.1:c.211G>A
NM_000162.4:c.214G>A
NM_001354800.1:c.214G>A
NM_033507.2:c.217G>A
NM_033508.2:c.211G>A
NM_033507.3:c.217G>A
NM_033508.3:c.211G>A

Pathogenic

Met criteria codes 7

PP1_Strong | PS3_Supporting | PS4 | PM2_Supporting | PP2 | PP3 | PP4_Moderate

Not Met criteria codes 1

PM1

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.214G>A variant in the glucokinase gene, GCK causes an amino acid change of glycine to arginine at codon 72 (p.(Gly72Arg)) 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 also predicted to be deleterious by computational evidence, with a REVEL score of 0.994, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copies in the African/African American subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in 48 unrelated individuals with diabetes/hyperglycemia (PS4; 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 OGTT increment < 3 mmol/L) (PP4_Moderate, internal lab contributors). This variant segregated with diabetes/hyperglycemia with 23 informative meioses in multiple families (PP1_Strong; internal lab contributors). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters passed the quality control, the wild-type ATP Km was between 0.4-0.65, the p.Gly72Arg had a relative activity index (RAI) > 0.5 and a relative stability index (RSI) <=0.5 (PS3_Supporting; PMID: 25015100). In summary, c.214G>A meets the criteria to be classified as Pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2.0, approved 8/11/2023): PS4, PP1_Strong, PP4_Moderate, PS3_Supporting, PM2_Supporting, PP3, PP2.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia with 23 informative meioses in multiple families (PP1_Strong; internal lab contributors).
PS3_Supporting	✔	A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters passed the quality control, the wild-type ATP Km was between 0.4-0.65, the p.Gly72Arg had a relative activity index (RAI) > 0.5 and a relative stability index (RSI) <=0.5 (PS3_Supporting; PMID: 25015100).
PS4	✔	This variant was identified in 48 unrelated individuals with diabetes/hyperglycemia (PS4; internal lab contributors).
PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copies in the African/African American subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (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 0.994, which is greater than the MDEP VCEP 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 OGTT increment < 3 mmol/L) (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

Curation History

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