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Variant: NM_000162.5(GCK):c.629T>A (p.Met210Lys)

Version: 1.0

CA204367

16141 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7277513a-d176-41fb-8fee-d6d0a2da162e
Approved on: 2023/7/30
Published on: 2023/7/30

HGVS expressions

NM_000162.5:c.629T>A
NM_000162.5(GCK):c.629T>A (p.Met210Lys)
NC_000007.14:g.44149810A>T
CM000669.2:g.44149810A>T
NC_000007.13:g.44189409A>T
CM000669.1:g.44189409A>T
NC_000007.12:g.44155934A>T
NG_008847.1:g.44614T>A
NG_008847.2:g.53361T>A
ENST00000395796.8:c.*627T>A
ENST00000616242.5:c.629T>A
ENST00000682635.1:n.1115T>A
ENST00000345378.7:c.632T>A
ENST00000403799.8:c.629T>A
ENST00000671824.1:c.629T>A
ENST00000673284.1:c.629T>A
ENST00000345378.6:c.632T>A
ENST00000395796.7:c.626T>A
ENST00000403799.7:c.629T>A
ENST00000437084.1:c.578T>A
ENST00000616242.4:c.626T>A
NM_000162.3:c.629T>A
NM_033507.1:c.632T>A
NM_033508.1:c.626T>A
NM_000162.4:c.629T>A
NM_001354800.1:c.629T>A
NM_033507.2:c.632T>A
NM_033508.2:c.626T>A
NM_033507.3:c.632T>A
NM_033508.3:c.626T>A

Pathogenic

Met criteria codes 8

PM2_Supporting | PP2 | PP3 | PM5 | PS3_Moderate | PP4_Moderate | PP1_Strong | PM3_Supporting

Not Met criteria codes 3

BA1 | BS1 | 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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.629T>A variant in the glucokinase gene, GCK, causes an amino acid change of methionine to lysine at codon 210 (p.(Met210Lys)) 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 threshold of 0.70 (PP3), and functional studies suggest that this variant alters glucokinase kinetic parameters, with an RAI less than 0.5 (wild-type QC parameters met including ATP Km between 0.4 and 0.65) (PS3_Moderate; PMIDs: 16731834,14517946). This variant was identified in two unrelated families with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMIDs:18399931, 11372010, 27913849, internal lab contributor). At least one individual individual had a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% persisting over time) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes, with at least 10 informative meioses in a family with MODY (PP1_Strong; PMIDs: 18399931, 11372010). This variant has also been detected in at least one family with neonatal diabetes. One individual in this family was homozygous and experienced permanent neonatal diabetes mellitus, and variants were were confirmed in trans (PM3_Supporting; PMIDs:18399931, 11372010). Additionally, another missense variant, c.629T>C (p.Met210Thr) has been interpreted as pathogenic by the ClinGen MDEP, and p.Met210Lyshas a greater Grantham distance (PM5). In summary, c.629T>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PP1_Strong, PM5, PP4_Moderate, PS3_Moderate, PP2, PP3, PM2_Supporting, PM3_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent in 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 threshold of 0.70 (PP3).
PM5	✔	Another missense variant, c.629T>C (p.Met210Thr) has been interpreted as pathogenic by the ClinGen MDEP, and p.Met210Lys has a greater Grantham distance (PM5).
PS3_Moderate	✔	Functional studies suggest that this variant alters glucokinase kinetic parameters, with an RAI less than 0.5 (wild type QC parameters met including ATP Km between 0.4 and 0.65) (PS3_Moderate; PMID: 16731834, PMID: 14517946).

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% persisting over time) (PP4_Moderate; internal lab contributors).
PP1_Strong	✔	This variant segregated with diabetes, with at least 10 informative meioses in a family with MODY (PP1_Strong; PMIDs:18399931, 11372010)
PM3_Supporting	✔	This variant has been detected in at least one family with neonatal diabetes. One individual in this family was homozygous and experienced permanent neonatal diabetes mellitus, and variants were confirmed in trans (PM3_Supporting; PMIDs:18399931, 11372010).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant was identified in two unrelated families with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID:18399931/PMID:11372010/PMID: 27913849, internal lab contributor).

Curation History

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