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Variant: NM_000162.5(GCK):c.410A>G (p.His137Arg)

Version: 1.0

CA367402077

2136527 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 1f10f058-0d0a-4ae8-b1c8-902f00adc777
Approved on: 2025/4/17
Published on: 2025/4/17

HGVS expressions

NM_000162.5:c.410A>G
NM_000162.5(GCK):c.410A>G (p.His137Arg)
NC_000007.14:g.44151029T>C
CM000669.2:g.44151029T>C
NC_000007.13:g.44190628T>C
CM000669.1:g.44190628T>C
NC_000007.12:g.44157153T>C
NG_008847.1:g.43395A>G
NG_008847.2:g.52142A>G
ENST00000395796.8:c.*408A>G
ENST00000616242.5:c.410A>G
ENST00000682635.1:n.896A>G
ENST00000345378.7:c.413A>G
ENST00000403799.8:c.410A>G
ENST00000671824.1:c.410A>G
ENST00000673284.1:c.410A>G
ENST00000345378.6:c.413A>G
ENST00000395796.7:c.407A>G
ENST00000403799.7:c.410A>G
ENST00000437084.1:c.364-5A>G
ENST00000616242.4:c.407A>G
NM_000162.3:c.410A>G
NM_033507.1:c.413A>G
NM_033508.1:c.407A>G
NM_000162.4:c.410A>G
NM_001354800.1:c.410A>G
NM_033507.2:c.413A>G
NM_033508.2:c.407A>G
NM_033507.3:c.413A>G
NM_033508.3:c.407A>G

Likely Pathogenic

Met criteria codes 4

PP2 | PP4_Moderate | PM2_Supporting | PP1_Strong

Not Met criteria codes 4

PS3 | PS4 | PP3 | BP4

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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.410A>G variant in the glucokinase gene, GCK, causes an amino acid change of histidine to arginine at codon 137 (p.(His137Arg)) 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). The variant is absent in gnomAD v2.1 and v4.1 (PM2_Supporting). It has a REVEL score of 0.598, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function. 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: 10525657, 14517946). This variant was identified in two unrelated cases with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID: 904948, internal lab contributors). One of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributor). Additionally, this variant segregated with hyperglycemia, with nine informative meioses in a single family (PP1_Strong; PMID: 9049484). In summary, c.410A>G meets the criteria to be classified as a likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 8/11/2023): PP1_Strong, PP4_Moderate, PM2_Supporting, PP2.

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).
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 negative antibodies) (PP4_Moderate; Internal lab contributor).
PM2_Supporting	✔	Absent in gnomAD v2.1 and v4.1 (PM2_Supporting).
PP1_Strong	✔	This variant segregated with hyperglycemia, with nine informative meioses in one family (PP1_Strong; PMID: 9049484).

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: 10525657, 14517946).

PS4		✖	This variant was identified in two unrelated cases 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: 904948, Internal lab contributors).
PP3		✖	This variant has a REVEL score of 0.598, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function.
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

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