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Variant: NM_000162.5(GCK):c.437T>C (p.Leu146Pro)

Version: 1.0

CA367401978

2428681 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: d4e06e06-f5e0-4a8d-82bb-81e4dbeb6520
Approved on: 2023/8/13
Published on: 2023/8/13

HGVS expressions

NM_000162.5:c.437T>C
NM_000162.5(GCK):c.437T>C (p.Leu146Pro)
NC_000007.14:g.44151002A>G
CM000669.2:g.44151002A>G
NC_000007.13:g.44190601A>G
CM000669.1:g.44190601A>G
NC_000007.12:g.44157126A>G
NG_008847.1:g.43422T>C
NG_008847.2:g.52169T>C
ENST00000395796.8:c.*435T>C
ENST00000616242.5:c.437T>C
ENST00000682635.1:n.923T>C
ENST00000345378.7:c.440T>C
ENST00000403799.8:c.437T>C
ENST00000671824.1:c.437T>C
ENST00000673284.1:c.437T>C
ENST00000345378.6:c.440T>C
ENST00000395796.7:c.434T>C
ENST00000403799.7:c.437T>C
ENST00000437084.1:c.386T>C
ENST00000616242.4:c.434T>C
NM_000162.3:c.437T>C
NM_033507.1:c.440T>C
NM_033508.1:c.434T>C
NM_000162.4:c.437T>C
NM_001354800.1:c.437T>C
NM_033507.2:c.440T>C
NM_033508.2:c.434T>C
NM_033507.3:c.440T>C
NM_033508.3:c.434T>C

Pathogenic

Met criteria codes 8

PS3_Moderate PM2_Supporting PS4_Moderate PM3 PP1 PP2 PP3 PP4

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 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.437T>C variant in the glucokinase gene, GCK causes an amino acid change of leucine to proline at codon 146 (p.(Leu146Pro)) 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 0.983, 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 was identified in 4 unrelated individuals with diabetes/hyperglycemia (PS4_Moderate; PMID: 25015100, 31441606, internal lab contributors). This variant segregated with diabetes/hyperglycemia with 3 informative meioses in 1 family (PP1; internal lab contributors). This variant has been detected in the homozygous state in at least 3 individuals with permanent neonatal diabetes (PP4 and PM3; PMIDs: 25015100, 31441606, internal lab contributor). A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Leu146Pro variant has a relative activity index (RAI) <0.50 (PS3_Moderate; PMID: 25015100). In summary, the c.437T>C variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.3.0, approved 8/11/2023): PS4_Moderate, PM3, PP4, PP1, PM2_Supporting, PP2, PP3, PS3_Moderate.

Met criteria codes

PS3_Moderate	✔	A kinetic analysis of recombinant wild-type (WT) and mutant glucokinase demonstrated that the wild-type kinetic parameters pass the quality control, the wild-type ATP Km is between 0.4-0.65, and the p.Leu146Pro variant has a relative activity index (RAI) <0.50 (PS3_Moderate; PMID: 25015100).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4_Moderate	✔	This variant was identified in 4 unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 25015100, 31441606, internal lab contributors).
PM3	✔	This variant has been detected in the homozygous state in at least 3 individuals with neonatal diabetes (PM3; PMIDs: 25015100, 31441606, internal lab contributor).
PP1	✔	This variant segregated with diabetes/hyperglycemia with 3 informative meioses in 1 family (PP1; internal lab contributors).
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 0.983, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4		✔	This variant was identified in in the homozygous state in 3 individual(s) with neonatal diabetes and negative testing for ABCC8, KCNJ11, and INS (PMIDs: 25015100, 31441602, internal lab contributors).

Curation History

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