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Variant: NM_000162.5(GCK):c.911T>C (p.Leu304Pro)

Version: 1.0

CA367400043

447425 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b5ed44bd-0988-4dfa-b8cb-386b405459c5
Approved on: 2023/8/9
Published on: 2023/8/10

HGVS expressions

NM_000162.5(GCK):c.911T>C (p.Leu304Pro)
NM_000162.5:c.911T>C
NC_000007.14:g.44146571A>G
CM000669.2:g.44146571A>G
NC_000007.13:g.44186170A>G
CM000669.1:g.44186170A>G
NC_000007.12:g.44152695A>G
NG_008847.1:g.47853T>C
NG_008847.2:g.56600T>C
ENST00000395796.8:c.*909T>C
ENST00000616242.5:c.*31T>C
ENST00000683378.1:n.137T>C
ENST00000345378.7:c.914T>C
ENST00000403799.8:c.911T>C
ENST00000671824.1:c.974T>C
ENST00000673284.1:c.911T>C
ENST00000345378.6:c.914T>C
ENST00000395796.7:c.908T>C
ENST00000403799.7:c.911T>C
ENST00000437084.1:c.860T>C
ENST00000473353.1:n.209T>C
ENST00000616242.4:c.908T>C
NM_000162.3:c.911T>C
NM_033507.1:c.914T>C
NM_033508.1:c.908T>C
NM_000162.4:c.911T>C
NM_001354800.1:c.911T>C
NM_001354801.1:c.8+48T>C
NM_033507.2:c.914T>C
NM_033508.2:c.908T>C
NM_033507.3:c.914T>C
NM_033508.3:c.908T>C

Pathogenic

Met criteria codes 7

PS4 PP2 PP3 PP4 PM2_Supporting PP1_Strong PS3_Moderate

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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.911T>C variant in the glucokinase gene, GCK, causes an amino acid change of leucine to proline at codon 304 (p.(Leu304Pro)) 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 0.874, which is greater than the MDEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF less than or equal to 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in 13 unrelated individuals with hyperglycemia (PS4; PMID 29207974, 11942313, internal lab contributors). This variant segregated with diabetes with 4 informative meioses in 3 families with diabetes/hyperglycemia (PP1_Strong; 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%) (PP4; internal lab contributors). 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.Leu304Pro variant has RAI=0.19, which is less than the MDEP VCEP threshold of 0.50. (PMIDs: 29704611, 26208450). In summary, this 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 1.2.0, approved 6/7/2023): PM2_Supporting, PP3, PP2, PP4, PS4, PP1_Strong, PS3_Supporting.

Met criteria codes

PS4	✔	This variant was identified in 13 unrelated individuals with hyperglycemia (PS4; PMID 29207974, 11942313, 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 0.874, which is greater than the MDEP threshold of 0.70 (PP3).
PP4	✔	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%) (PP4; internal lab contributors).
PM2_Supporting	✔	variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copies in any other subpopulation, thereby meeting the ClinGen MDEP threshold

criteria for PM2_Supporting (ENF Popmax FAF less than or equal to 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).

PP1_Strong	✔	This variant segregated with diabetes with 4 informative meioses in 3 families with diabetes/hyperglycemia (PP1_Strong; internal lab contributors).
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.Leu304Pro variant has RAI=0.19, which is less than the MDEP VCEP threshold of 0.50. (PMIDs: 29704611, 26208450)

Curation History

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