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Variant: NM_033508.3:c.110A>T

Version: 1.0

CA367403522

2691828 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 6872d9e4-b4bd-41fa-b4a1-0b46087ff8f1
Approved on: 2024/1/5
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HGVS expressions

NM_033508.3:c.110A>T
NC_000007.14:g.44153396T>A
CM000669.2:g.44153396T>A
NC_000007.13:g.44192995T>A
CM000669.1:g.44192995T>A
NC_000007.12:g.44159520T>A
NG_008847.1:g.41028A>T
NG_008847.2:g.49775A>T
ENST00000395796.8:c.*111A>T
ENST00000616242.5:c.113A>T
ENST00000682635.1:n.599A>T
ENST00000345378.7:c.116A>T
ENST00000403799.8:c.113A>T
ENST00000671824.1:c.113A>T
ENST00000673284.1:c.113A>T
ENST00000345378.6:c.116A>T
ENST00000395796.7:c.110A>T
ENST00000403799.7:c.113A>T
ENST00000437084.1:c.113A>T
ENST00000476008.1:n.548A>T
ENST00000616242.4:c.110A>T
NM_000162.3:c.113A>T
NM_033507.1:c.116A>T
NM_033508.1:c.110A>T
NM_000162.4:c.113A>T
NM_001354800.1:c.113A>T
NM_033507.2:c.116A>T
NM_033508.2:c.110A>T
NM_000162.5:c.113A>T
NM_033507.3:c.116A>T

Likely Pathogenic

Met criteria codes 4

PP2 PM5 PP4_Moderate PM2_Supporting

Not Met criteria codes 4

PP1 PP3 PM1 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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.113A>T variant in the glucokinase gene, GCK, causes an amino acid change of glutamine to leucine at codon 38 (p.(Gln38Leu)) 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 has a REVEL score of 0.657, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). 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; PMID: 24550216, internal lab contributors). This variant segregated with hyperglycemia with 1 informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 24550216, internal lab contributors). Another missense variant, c.113A>C p.Gln38Pro, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gln38Leu has a greater Grantham distance (PM5). In summary, c.113A>T meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP4_Moderate, PM5, PP2, PM2_Supporting.

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).
PM5	✔	Another missense variant, c.113A>C p.Gln38Pro, has been interpreted as pathogenic by the ClinGen MDEP, and p.Gln38Leu has a greater Grantham distance (PM5).
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; PMID: 24550216, internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PP1	✖	This variant segregated with hyperglycemia with 1 informative meiosis in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 24550216, internal lab contributors).

PP3		✖	This variant has a REVEL score of 0.657, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function.
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	This variant has a REVEL score of 0.657, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on GCK function.

Curation History

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