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Variant: NM_033508.3:c.106A>G

Version: 1.0

CA367403551

2664358 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 9f2f23c4-3ce8-40f2-ae5b-5e511452ce17
Approved on: 2023/11/22
Published on: 2023/11/22

HGVS expressions

NM_033508.3:c.106A>G
NC_000007.14:g.44153400T>C
CM000669.2:g.44153400T>C
NC_000007.13:g.44192999T>C
CM000669.1:g.44192999T>C
NC_000007.12:g.44159524T>C
NG_008847.1:g.41024A>G
NG_008847.2:g.49771A>G
ENST00000395796.8:c.*107A>G
ENST00000616242.5:c.109A>G
ENST00000682635.1:n.595A>G
ENST00000345378.7:c.112A>G
ENST00000403799.8:c.109A>G
ENST00000671824.1:c.109A>G
ENST00000673284.1:c.109A>G
ENST00000345378.6:c.112A>G
ENST00000395796.7:c.106A>G
ENST00000403799.7:c.109A>G
ENST00000437084.1:c.109A>G
ENST00000476008.1:n.544A>G
ENST00000616242.4:c.106A>G
NM_000162.3:c.109A>G
NM_033507.1:c.112A>G
NM_033508.1:c.106A>G
NM_000162.4:c.109A>G
NM_001354800.1:c.109A>G
NM_033507.2:c.112A>G
NM_033508.2:c.106A>G
NM_000162.5:c.109A>G
NM_033507.3:c.112A>G

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

PP1

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.109A>G variant in the glucokinase gene, GCK, causes an amino acid change of methionine to valine at codon 37 (p.(Met37Val)) of NM_000162.5.This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributor). 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 0.8759, which is greater than the MDEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). Another missense variant, c.110T>G (p.Met37Arg) has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Met37Val (PM5_Supporting). This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918; internal lab contributor). In summary, c.109A>G 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, PP2, PP3, PM2_Supporting, PM5_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).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.8759, which is greater than the MDEP threshold of 0.70 (PP3).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributor).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.110T>G (p.Met37Arg) has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Met37Val (PM5_Supporting).

Not Met criteria codes

PP1	✖	

This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918; internal lab contributor).

Curation History

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