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Variant: NM_000162.5(GCK):c.1163G>A (p.Gly388Asp)

Version: 1.0

CA367398670

995101 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e2b51e72-7014-4bfd-aa41-30e5318337fe
Approved on: 2023/12/2
Published on: 2023/12/2

HGVS expressions

NM_000162.5(GCK):c.1163G>A (p.Gly388Asp)
NM_000162.5:c.1163G>A
NC_000007.14:g.44145587C>T
CM000669.2:g.44145587C>T
NC_000007.13:g.44185186C>T
CM000669.1:g.44185186C>T
NC_000007.12:g.44151711C>T
NG_008847.1:g.48837G>A
NG_008847.2:g.57584G>A
ENST00000395796.8:c.*1161G>A
ENST00000616242.5:c.*283G>A
ENST00000683378.1:n.389G>A
ENST00000336642.9:c.197G>A
ENST00000345378.7:c.1166G>A
ENST00000403799.8:c.1163G>A
ENST00000671824.1:c.1226G>A
ENST00000672743.1:n.175G>A
ENST00000673284.1:c.1163G>A
ENST00000336642.8:c.215G>A
ENST00000345378.6:c.1166G>A
ENST00000395796.7:c.1160G>A
ENST00000403799.7:c.1163G>A
ENST00000437084.1:c.1112G>A
ENST00000459642.1:n.543G>A
ENST00000616242.4:c.1160G>A
NM_000162.3:c.1163G>A
NM_033507.1:c.1166G>A
NM_033508.1:c.1160G>A
NM_000162.4:c.1163G>A
NM_001354800.1:c.1163G>A
NM_001354801.1:c.152G>A
NM_001354802.1:c.23G>A
NM_001354803.1:c.197G>A
NM_033507.2:c.1166G>A
NM_033508.2:c.1160G>A
NM_033507.3:c.1166G>A
NM_033508.3:c.1160G>A

NM_001354803.2:c.197G>A

Pathogenic

Met criteria codes 7

PS4 PP2 PP3 PS2_Moderate PP4_Moderate PM2_Supporting PP1_Moderate

Not Met criteria codes 1

PM1

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.1163G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to aspartic acid at codon 388 (p.(Gly388Asp)) 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 0.871, 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 8 unrelated individuals with hyperglycemia (PS4; PMID:35737141, 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 contributors). Another one of these individuals was identified as a de novo occurrence with confirmed parental relationships whose clinical picture was consistent with but not highly specific for GCK-hyperglycemia (PS2_Moderate; internal lab contributors). This variant segregated with hyperglycemia, with 3 informative meioses in 3 families (PP1_Moderate; internal lab contributors). In summary, c.1163G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3, approved 8/11/2023): PS4, PP1_Moderate, PP4_Moderate, PS2_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PS4	✔	This variant was identified in 8 unrelated individuals with hyperglycemia (PS4; PMID: 35737141, 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 0.871, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS2_Moderate	✔	This variant was identified as a de novo occurrence with confirmed parental relationships in whose clinical picture is consistent with but not highly specific for GCK-hyperglycemia (PS2_Moderate; internal lab contributors).
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 contributors).

PM2_Supporting		✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP1_Moderate		✔	This variant segregated with hyperglycemia, with 3 informative meioses in 2 families (PP1_Moderate; internal lab contributors).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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