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Variant: NM_000162.5(GCK):c.128G>A (p.Arg43His)

Version: 1.0

CA4239718

393453 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: dd64642b-fad9-40c9-a9ea-0b3de810cdff
Approved on: 2023/8/25
Published on: 2023/8/25

HGVS expressions

NM_000162.5(GCK):c.128G>A (p.Arg43His)
NM_000162.5:c.128G>A
NC_000007.14:g.44153381C>T
CM000669.2:g.44153381C>T
NC_000007.13:g.44192980C>T
CM000669.1:g.44192980C>T
NC_000007.12:g.44159505C>T
NG_008847.1:g.41043G>A
NG_008847.2:g.49790G>A
ENST00000395796.8:c.*126G>A
ENST00000616242.5:c.128G>A
ENST00000682635.1:n.614G>A
ENST00000345378.7:c.131G>A
ENST00000403799.8:c.128G>A
ENST00000671824.1:c.128G>A
ENST00000673284.1:c.128G>A
ENST00000345378.6:c.131G>A
ENST00000395796.7:c.125G>A
ENST00000403799.7:c.128G>A
ENST00000437084.1:c.128G>A
ENST00000616242.4:c.125G>A
NM_000162.3:c.128G>A
NM_033507.1:c.131G>A
NM_033508.1:c.125G>A
NM_000162.4:c.128G>A
NM_001354800.1:c.128G>A
NM_033507.2:c.131G>A
NM_033508.2:c.125G>A
NM_033507.3:c.131G>A
NM_033508.3:c.125G>A

Pathogenic

Met criteria codes 7

PP2 PP3 PP1_Moderate PS4 PP4_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

PS3

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.128G>A variant in the glucokinase gene, GCK, causes an amino acid change of arginine to histidine at codon 43 (p.(Arg43His)) 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 0.8159, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Functional studies demonstrated that the p.Arg43His variant has normal relative activity index (RAI>0.5) and normal GKA/GKRP interaction; however the relative stability index (RSI) was not calculated and therefore neither PS3 or BS3 can be applied (PMID: 22611063). This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the Latino/Admixed American subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in eight unrelated individuals with hyperglycemia (PS4; PMIDs: 11942313, 22611063, 27106716, 25015100, 22493702, 30245511, 31638168, 33046911). 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: 30245511). This variant segregated with diabetes/hyperglycemia, with three informative meioses in two families (PP1_Moderate; PMIDs: 22611063, 22493702). Another missense variant, c.127C>T (p.Arg43Cys), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Arg43His (PM5_Supporting). In summary, the c.128G>A variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified for by the GlinGen MDEP (specification version 1.3.0, approved 8/11/2023): PS4, PP4_Moderate, PP1_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 0.8159, which is greater than or equal to the MDEP VCEP threshold of 0.70 (PP3).
PP1_Moderate	✔	This variant segregated with diabetes/hyperglycemia, with three informative meioses in two families (PP1_Moderate; PMIDs: 22611063, 22493702).
PS4	✔	This variant was identified in eight unrelated individuals with hyperglycemia (PS4; PMIDs: 11942313, 22611063, 27106716, 25015100, 22493702, 30245511, 31638168, 33046911).
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: 30245511).

PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the Latino/Admixed American subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.127C>T (p.Arg43Cys), has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Arg43His (PM5_Supporting).

Not Met criteria codes

PS3	✖	Functional studies demonstrated that the p.Arg43His variant has normal relative activity index (RAI>0.5) and normal GKA/GKRP interaction; however the RSI was not calculated and therefore neither PS3 or BS3 can be applied.

Curation History

Showing 1 to 1 of 1 rows

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