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Variant: NM_000162.5(GCK):c.775G>A (p.Ala259Thr)

Version: 1.0

CA367400584

435302 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 7c9a6580-e9be-4685-b711-9d54c57cf1f2
Approved on: 2023/8/12
Published on: 2023/8/12

HGVS expressions

NM_000162.5(GCK):c.775G>A (p.Ala259Thr)
NM_000162.5:c.775G>A
NC_000007.14:g.44147738C>T
CM000669.2:g.44147738C>T
NC_000007.13:g.44187337C>T
CM000669.1:g.44187337C>T
NC_000007.12:g.44153862C>T
NG_008847.1:g.46686G>A
NG_008847.2:g.55433G>A
ENST00000395796.8:c.*773G>A
ENST00000616242.5:c.775G>A
ENST00000345378.7:c.778G>A
ENST00000403799.8:c.775G>A
ENST00000671824.1:c.775G>A
ENST00000673284.1:c.775G>A
ENST00000345378.6:c.778G>A
ENST00000395796.7:c.772G>A
ENST00000403799.7:c.775G>A
ENST00000437084.1:c.724G>A
ENST00000616242.4:c.772G>A
NM_000162.3:c.775G>A
NM_033507.1:c.778G>A
NM_033508.1:c.772G>A
NM_000162.4:c.775G>A
NM_001354800.1:c.775G>A
NM_033507.2:c.778G>A
NM_033508.2:c.772G>A
NM_033507.3:c.778G>A
NM_033508.3:c.772G>A

Pathogenic

Met criteria codes 7

PP2 PP3 PP1_Strong PS4 PP4_Moderate PM2_Supporting PM5_Supporting

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Not Met criteria codes 1

PM1

Evidence Links 0

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.775G>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to threonine at codon 259 (p.(Ala259Thr)) of NM_000162.5. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.948, which is greater than the MDEP VCEP threshold of 0.70 (PP3) and is absent from gnomAD v2.1.1 (PM2_Supporting). 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). Another missense variant, c.776C>T, p.Ala259Val, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ala259Thr (PM5_Supporting). This variant was identified in 12 unrelated individuals with hyperglycemia (PS4; internal lab contributors). Additionally, this variant segregated with diabetes/hyperglycemia, with 7 informative meioses in 6 families (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% and a 3-generation family history of diabetes) (PP4_Moderate; internal lab contributors). In summary, c.775G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP3, PP2, PM5_Supporting, PS4, PP1_Strong, PP4_Moderate, 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).
PP3	✓	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.901, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong	✓	This variant segregated with diabetes/hyperglycemia, with 7 informative meioses in 6 families (PP1_Strong; internal lab contributors).
PS4	✓	This variant was identified in 12 unrelated individuals with hyperglycemia (PS4; 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 a 3-generation family history of diabetes) (PP4_Moderate; internal lab contributors).
PM2_Supporting	✓	This variant has an incomputable gnomAD v2.1.1 Popmax minor filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the South Asian 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.776C>T p.Ala259Val, has been classified as pathogenic by the ClinGen MDEP but has a greater Grantham distance than p.Ala259Thr (PM5_Supporting).

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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