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Variant: NM_000162.5(GCK):c.683C>T (p.Thr228Met)

Version: 1.0

CA260620

16134 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5ffe0ec7-6736-4676-bf37-412af923d449
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HGVS expressions

NM_000162.5:c.683C>T
NM_000162.5(GCK):c.683C>T (p.Thr228Met)
NC_000007.14:g.44147830G>A
CM000669.2:g.44147830G>A
NC_000007.13:g.44187429G>A
CM000669.1:g.44187429G>A
NC_000007.12:g.44153954G>A
NG_008847.1:g.46594C>T
NG_008847.2:g.55341C>T
ENST00000395796.8:c.*681C>T
ENST00000616242.5:c.683C>T
ENST00000345378.7:c.686C>T
ENST00000403799.8:c.683C>T
ENST00000671824.1:c.683C>T
ENST00000673284.1:c.683C>T
ENST00000345378.6:c.686C>T
ENST00000395796.7:c.680C>T
ENST00000403799.7:c.683C>T
ENST00000437084.1:c.632C>T
ENST00000616242.4:c.680C>T
NM_000162.3:c.683C>T
NM_033507.1:c.686C>T
NM_033508.1:c.680C>T
NM_000162.4:c.683C>T
NM_001354800.1:c.683C>T
NM_033507.2:c.686C>T
NM_033508.2:c.680C>T
NM_033507.3:c.686C>T
NM_033508.3:c.680C>T

Pathogenic

Met criteria codes 10

PS3_Supporting PM3_Supporting PM2_Supporting PP4_Moderate PM1 PS2 PS4 PP2 PP3 PP1_Strong

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

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.683C>T variant in the glucokinase gene, GCK, causes an amino acid change of threonine to methionine at codon 228 (p.(Thr228Met)) 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 resides in an amino acid that directly binds glucose and ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.966 which is greater than the MDEP VCEP threshold of 0.70 (PP3). In an assay in which the ATPkm was above the MDEP threshold for evaluation of relative activity index (RAI), the Kcat/S0.5 ratio of the Thr228Met variant was 0.0001, which is less than 0.5 of wild type (PS3_Supporting; PMID: 11372010). This variant has an incomputable gnomAD v2.1.1 Grpmax 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 at least 26 unrelated individuals with hyperglycemia (PS4; PMIDs: 21720051, 2721189, 36836406, 36723869, 32741144, 34756319, 11372010, 1502186, 31639168, 24323243, internal lab contributors). At least 2 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; PMID: 36723869). This variant was identified as a de novo occurrence with confirmed parental relationships in an individual with a clinical picture highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6-7.6 and negative antibodies) (PS2; PMID: 24323243). This variant has been detected in one individual with neonatal diabetes who was found to be homozygous for the c.683C>T variant (PM3_Supporting; PMID: 11372010). In summary, c.683C>T 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, PS2, PP4_Moderate, PM1, PP2, PP3, PM2_Supporting, PM3_Supporting, PS3_Supporting.

Met criteria codes

PS3_Supporting ✔	In an assay in which the ATPkm was above the MDEP threshold for evaluation of relative activity index (RAI), the Kcat/S0.5 ratio of the Thr228Met variant was 0.0001, which is less than 0.5 of wild type (PS3_Supporting; PMID: 11372010).
PM3_Supporting ✔	This variant has been detected in one individual with neonatal diabetes who was found to be homozygous for the c.683C>T variant (PM3_Supporting, PMID: 11372010).
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).
PP4_Moderate ✔	This variant was identified in 2 individuals 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; PMID: 36723869, 24323243).
PM1 ✔	This variant resides in an amino acid that directly binds glucose and ATP, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
PS2 ✔	This variant was identified as a de novo occurrence with confirmed parental relationships in an individual with a clinical picture highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6-7.6 and negative antibodies) (PS2; PMID: 24323243).
PS4 ✔	This variant was identified in at least 26 unrelated individuals with hyperglycemia (PS4; PMIDs: 21720051, 2721189, 36836406, 36723869, 32741144, 34756319, 11372010, 1502186, 31639168, 24323243). Additional data from Paris?

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 0.966 which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong		✔	This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in 2 families (PP1_Strong; PMIDs: 1502186, 27271189).

Curation History

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