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Variant: NM_000162.5(GCK):c.1160C>T (p.Ala387Val)

Version: 1.1

CA213727

36182 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 73712264-65e3-4f09-bf55-c8058854d12f
Approved on: 2024/2/28
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HGVS expressions

NM_000162.5:c.1160C>T
NM_000162.5(GCK):c.1160C>T (p.Ala387Val)
NC_000007.14:g.44145590G>A
CM000669.2:g.44145590G>A
NC_000007.13:g.44185189G>A
CM000669.1:g.44185189G>A
NC_000007.12:g.44151714G>A
NG_008847.1:g.48834C>T
NG_008847.2:g.57581C>T
ENST00000395796.8:c.*1158C>T
ENST00000616242.5:c.*280C>T
ENST00000683378.1:n.386C>T
ENST00000336642.9:c.194C>T
ENST00000345378.7:c.1163C>T
ENST00000403799.8:c.1160C>T
ENST00000671824.1:c.1223C>T
ENST00000672743.1:n.172C>T
ENST00000673284.1:c.1160C>T
ENST00000336642.8:c.212C>T
ENST00000345378.6:c.1163C>T
ENST00000395796.7:c.1157C>T
ENST00000403799.7:c.1160C>T
ENST00000437084.1:c.1109C>T
ENST00000459642.1:n.540C>T
ENST00000616242.4:c.1157C>T
NM_000162.3:c.1160C>T
NM_033507.1:c.1163C>T
NM_033508.1:c.1157C>T
NM_000162.4:c.1160C>T
NM_001354800.1:c.1160C>T
NM_001354801.1:c.149C>T
NM_001354802.1:c.20C>T
NM_001354803.1:c.194C>T
NM_033507.2:c.1163C>T
NM_033508.2:c.1157C>T
NM_033507.3:c.1163C>T
NM_033508.3:c.1157C>T

NM_001354803.2:c.194C>T

Pathogenic

Met criteria codes 7

PS4_Moderate PP2 PP3 PM5 PP4_Moderate PM2_Supporting PP1_Strong

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.1160C>T variant in the glucokinase gene, GCK, causes an amino acid change of alanine to valine at codon 387 (p. (Ala387Val)) of NM_000162.5. This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to no copies in the European non-Finnish subpopulation and one copy in any other 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). 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 located in the larger hexokinase domain of the GCK gene (PMID: 31638168) but this variant does not reside in an amino acid that directly binds glucose or ATP, which is defined as critical for the protein's function by the ClinGen MDEP, so it does not meet PM1. 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). Another missense variant, c.1159G>A p.(Ala387Thr) has been interpreted as pathogenic by the ClinGen MDEP, and p.Ala387Glu has a greater Grantham distance (PM5). This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 34421822, 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; PMID: 34421822). This variant segregated with hyperglycemia, with five informative meioses in three families (PP1_Strong; PMID: 34421822, Internal lab contributor). In summary, c.1160C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (VCEP specifications version v1.3.0; approved 8/11/2023): PP2, PP3, PM2_Supporting, PP1_Strong, PM5, PS4_Moderate, PP4_Moderate.

Met criteria codes

PS4_Moderate	✔	This variant was identified in four unrelated individuals with hyperglycemia (PS4_Moderate; PMID: 34421822, 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	✔	REVEL 0.871
PM5	✔	Another missense variant, c.1159G>A p.(Ala387Thr) has been interpreted as pathogenic by the ClinGen MDEP, and p.Ala387Val has a greater Grantham distance (PM5).

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; PMID: 34421822).
PM2_Supporting		✔	This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to no copies in the European non-Finnish subpopulation and one copy in any other 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).
PP1_Strong		✔	This variant segregated with hyperglycemia, with five informative meioses in three families (PP1_Strong; PMID: 34421822, Internal lab contributor).

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

Showing 1 to 2 of 2 rows

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