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Variant: NM_001354803.2:c.336C>A

Version: 1.0

CA367397114

2571654 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: b73ffb72-dd55-4174-be2f-2f70fd4e971d
Approved on: 2023/6/25
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HGVS expressions

NM_001354803.2:c.336C>A
NC_000007.14:g.44145232G>T
CM000669.2:g.44145232G>T
NC_000007.13:g.44184831G>T
CM000669.1:g.44184831G>T
NC_000007.12:g.44151356G>T
NG_008847.1:g.49192C>A
NG_008847.2:g.57939C>A
ENST00000395796.8:c.*1300C>A
ENST00000616242.5:c.*422C>A
ENST00000683378.1:n.528C>A
ENST00000336642.9:c.336C>A
ENST00000345378.7:c.1305C>A
ENST00000403799.8:c.1302C>A
ENST00000671824.1:c.1365C>A
ENST00000672743.1:n.314C>A
ENST00000673284.1:c.1302C>A
ENST00000336642.8:c.354C>A
ENST00000345378.6:c.1305C>A
ENST00000395796.7:c.1299C>A
ENST00000403799.7:c.1302C>A
ENST00000437084.1:c.1251C>A
ENST00000459642.1:n.682C>A
ENST00000616242.4:c.1299C>A
NM_000162.3:c.1302C>A
NM_033507.1:c.1305C>A
NM_033508.1:c.1299C>A
NM_000162.4:c.1302C>A
NM_001354800.1:c.1302C>A
NM_001354801.1:c.291C>A
NM_001354802.1:c.162C>A
NM_001354803.1:c.336C>A
NM_033507.2:c.1305C>A
NM_033508.2:c.1299C>A
NM_000162.5:c.1302C>A
NM_033507.3:c.1305C>A
NM_033508.3:c.1299C>A

Pathogenic

Met criteria codes 5

PVS1 | PP4_Moderate | PP1_Strong | PM2_Supporting | PS4_Moderate

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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1302C>A variant in the glucokinase gene, GCK, results in a premature termination at codon 434 (p.(Cys434Ter)) of NM_000162.5. While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). This variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in 4 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID 28726111, PMID 19564454, internal lab contributor). One of these individuals had a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID 28726111). Additionally, this variant segregated with diabetes with 5 informative meioses in 2 families with MODY (PP1_Strong; PMID:28726111, internal lab contributor). In summary, the c.1302C>A variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PVS1, PP1_Strong, PP4_moderate, PS4_moderate, PM2_Supporting).

Met criteria codes

PVS1 ✔	While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1; PMID: 19790256).
PP4_Moderate ✔	This variant was identified in an individual with a clinical history highly specific for GCK-MODY ((FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID 28726111)
PP1_Strong ✔	This variant segregated with diabetes with 5 informative meioses in 2 families with MODY (PP1_Strong; PMID:28726111, internal lab contributor).
PM2_Supporting ✔	Absent in gnomAD v2.1.1 (PM2_Supporting).
PS4_Moderate ✔	This variant was identified in 4 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID 28726111, PMID 19564454, internal lab contributor).

Curation History

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