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Variant: NM_001354803.2:c.380_396del

Version: 1.0

CA2017997776

2571646 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: bd3084d6-9dc3-41fd-aa91-9835ae812ea8
Approved on: 2023/6/24
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HGVS expressions

NM_001354803.2:c.380_396del
NC_000007.14:g.44145176_44145192del
CM000669.2:g.44145176_44145192del
NC_000007.13:g.44184775_44184791del
CM000669.1:g.44184775_44184791del
NC_000007.12:g.44151300_44151316del
NG_008847.1:g.49236_49252del
NG_008847.2:g.57983_57999del
ENST00000395796.8:c.*1344_*1360del
ENST00000616242.5:c.*466_*482del
ENST00000683378.1:n.572_588del
ENST00000336642.9:c.380_396del
ENST00000345378.7:c.1349_1365del
ENST00000403799.8:c.1346_1362del
ENST00000671824.1:c.1409_1425del
ENST00000672743.1:n.358_374del
ENST00000673284.1:c.1346_1362del
ENST00000336642.8:c.398_414del
ENST00000345378.6:c.1349_1365del
ENST00000395796.7:c.1343_1359del
ENST00000403799.7:c.1346_1362del
ENST00000437084.1:c.1295_1311del
ENST00000459642.1:n.726_742del
ENST00000616242.4:c.1343_1359del
NM_000162.3:c.1346_1362del
NM_033507.1:c.1349_1365del
NM_033508.1:c.1343_1359del
NM_000162.4:c.1346_1362del
NM_001354800.1:c.1346_1362del
NM_001354801.1:c.335_351del
NM_001354802.1:c.206_222del
NM_001354803.1:c.380_396del
NM_033507.2:c.1349_1365del
NM_033508.2:c.1343_1359del
NM_000162.5:c.1346_1362del
NM_033507.3:c.1349_1365del
NM_033508.3:c.1343_1359del

Pathogenic

Met criteria codes 5

PS4_Moderate PP1 PP4 PVS1 PM2_Supporting

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.1346_1362del variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 449 (NM_000162.5), adding 4 novel amino acids before encountering a stop codon (p.(Ala449GlyfsTer4)). 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 (PM2_Supporting). This variant was identified in 5 unrelated individuals with a clinical picture consistent with non-autoimmune/insulin-deficient diabetes (PS4_Moderate; internal lab contributors). This variant was identified in at least two individuals with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4_Moderate, internal lab contributors). This variant segregated with disease with 2 informative meioses in 2 families with MODY (PP1; internal lab contributors). In summary, the c.1346_1362del 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, PP4, PS4_Moderate, PP1, PM2_Supporting.

Met criteria codes

PS4_Moderate ✔	This variant was identified in 5 unrelated individuals with a clinical picture consistent with non-autoimmune/insulin-deficient diabetes (PS4_Moderate; internal lab contributors)
PP1 ✔	This variant segregated with disease with 2 informative meioses in 2 families with MODY (PP1; internal lab contributors).
PP4 ✔	This variant was identified in at least two individuals with a clinical history highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4_Moderate, internal lab contributors).
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).
PM2_Supporting ✔	Absent in gnomAD v2.1.1 (PM2_Supporting).

Curation History

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