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Variant: NM_001354803.2:c.295del

Version: 1.0

CA2018007672

2571657 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 0c341913-df27-4583-812e-f7e5e0c9d34a
Approved on: 2023/6/26
Published on: 2023/6/26

HGVS expressions

NM_001354803.2:c.295del
NC_000007.14:g.44145274del
CM000669.2:g.44145274del
NC_000007.13:g.44184873del
CM000669.1:g.44184873del
NC_000007.12:g.44151398del
NG_008847.1:g.49151del
NG_008847.2:g.57898del
ENST00000395796.8:c.*1259del
ENST00000616242.5:c.*381del
ENST00000683378.1:n.487del
ENST00000336642.9:c.295del
ENST00000345378.7:c.1264del
ENST00000403799.8:c.1261del
ENST00000671824.1:c.1324del
ENST00000672743.1:n.273del
ENST00000673284.1:c.1261del
ENST00000336642.8:c.313del
ENST00000345378.6:c.1264del
ENST00000395796.7:c.1258del
ENST00000403799.7:c.1261del
ENST00000437084.1:c.1210del
ENST00000459642.1:n.641del
ENST00000616242.4:c.1258del
NM_000162.3:c.1261del
NM_033507.1:c.1264del
NM_033508.1:c.1258del
NM_000162.4:c.1261del
NM_001354800.1:c.1261del
NM_001354801.1:c.250del
NM_001354802.1:c.121del
NM_001354803.1:c.295del
NM_033507.2:c.1264del
NM_033508.2:c.1258del
NM_000162.5:c.1261del
NM_033507.3:c.1264del
NM_033508.3:c.1258del

Pathogenic

Met criteria codes 3

PP4 PVS1 PM2_Supporting

Not Met criteria codes 1

PS4

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.1261del variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 421 (NM_000162.5), adding 10 novel amino acids before encountering a stop codon (p.(Glu421SerfsTer10)). 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). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). This variant was identified in one individual with non-autoimmune or non-absolute/near-absolute insulin-deficient diabetes/hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID 16965331). However, the clinical history for this individual is highly specific for GCK-MODY (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; PMID: 16965331). Taken together, this evidence supports the classification of this variant as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP VCEP (specification version 1.2, approved 6/7/2023: PVS1, PM2_Supporting, PP4.

Met criteria codes

PP4	✔	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%) (PP4; PMID: 16965331).
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)
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting)

Not Met criteria codes

PS4	✖	This variant was identified in one individual who does not have autoimmune or absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (PMID 16965331).

Curation History

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