The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001354803.2:c.412del

Version: 1.0

CA2573102978

2571655 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: maturity-onset diabetes of the young type 2 (MONDO:0007453)
Inheritance Mode: Semidominant inheritance
UUID: 44ebdc11-ff37-4204-814b-b927afcb97ea
Approved on: 2023/6/18
Published on: 2023/6/18

HGVS expressions

NM_001354803.2:c.412del
NC_000007.14:g.44145157del
CM000669.2:g.44145157del
NC_000007.13:g.44184756del
CM000669.1:g.44184756del
NC_000007.12:g.44151281del
NG_008847.1:g.49268del
NG_008847.2:g.58015del
ENST00000395796.8:c.*1376del
ENST00000616242.5:c.*498del
ENST00000683378.1:n.604del
ENST00000336642.9:c.412del
ENST00000345378.7:c.1381del
ENST00000403799.8:c.1378del
ENST00000671824.1:c.1441del
ENST00000672743.1:n.381+9del
ENST00000673284.1:c.1369+9del
ENST00000336642.8:c.430del
ENST00000345378.6:c.1381del
ENST00000395796.7:c.1375del
ENST00000403799.7:c.1378del
ENST00000437084.1:c.1327del
ENST00000459642.1:n.758del
ENST00000616242.4:c.1375del
NM_000162.3:c.1378del
NM_033507.1:c.1381del
NM_033508.1:c.1375del
NM_000162.4:c.1378del
NM_001354800.1:c.1369+9del
NM_001354801.1:c.367del
NM_001354802.1:c.229+9del
NM_001354803.1:c.412del
NM_033507.2:c.1381del
NM_033508.2:c.1375del
NM_000162.5:c.1378del
NM_033507.3:c.1381del
NM_033508.3:c.1375del

Pathogenic

Met criteria codes 3

PVS1 PM2_Supporting PP4_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.1378del variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 460 (NM_000162.5), adding 154 novel amino acids before encountering a stop codon (p.(Ala460ProfsTer154)). This variant, located in exon 10 of 10, is predicted to cause loss of a stop codon and result in an elongated protein. The additional residues are expected to cause improper folding, resulting in loss-of-function in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID 19790256). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). 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 antibody negative) (PP4_Moderate; PMID: 15841481). In summary, c.1378del 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, PM2_supporting, PP4_Moderate.

Met criteria codes

PVS1	✔	This variant, located in exon 10 of 10, is predicted to cause loss of a stop codon and result in an elongated protein. The additional residues are expected to cause improper folding, resulting in loss of function in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID 19790256).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
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 antibody negative) (PP4_Moderate; PMID: 15841481).

Curation History

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