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Variant: NM_001354803.2:c.166_167del

Version: 1.0

CA2580612101

3234000 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: e48e2a42-8d22-41bb-94c0-c92f02b352c6
Approved on: 2024/4/28
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HGVS expressions

NM_001354803.2:c.166_167del
NC_000007.14:g.44145622_44145623del
CM000669.2:g.44145622_44145623del
NC_000007.13:g.44185221_44185222del
CM000669.1:g.44185221_44185222del
NC_000007.12:g.44151746_44151747del
NG_008847.1:g.48806_48807del
NG_008847.2:g.57553_57554del
ENST00000395796.8:c.*1130_*1131del
ENST00000616242.5:c.*252_*253del
ENST00000683378.1:n.358_359del
ENST00000336642.9:c.166_167del
ENST00000345378.7:c.1135_1136del
ENST00000403799.8:c.1132_1133del
ENST00000671824.1:c.1195_1196del
ENST00000672743.1:n.144_145del
ENST00000673284.1:c.1132_1133del
ENST00000336642.8:c.184_185del
ENST00000345378.6:c.1135_1136del
ENST00000395796.7:c.1129_1130del
ENST00000403799.7:c.1132_1133del
ENST00000437084.1:c.1081_1082del
ENST00000459642.1:n.512_513del
ENST00000616242.4:c.1129_1130del
NM_000162.3:c.1132_1133del
NM_033507.1:c.1135_1136del
NM_033508.1:c.1129_1130del
NM_000162.4:c.1132_1133del
NM_001354800.1:c.1132_1133del
NM_001354801.1:c.121_122del
NM_001354802.1:c.-9_-8del
NM_001354803.1:c.166_167del
NM_033507.2:c.1135_1136del
NM_033508.2:c.1129_1130del
NM_000162.5:c.1132_1133del
NM_033507.3:c.1135_1136del
NM_033508.3:c.1129_1130del

Likely Pathogenic

Met criteria codes 2

PVS1 PM2_Supporting

Not Met criteria codes 2

PP1 PP4

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.1132_1133del variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 378 in NM_000162.5, adding 80 novel amino acids before encountering a stop codon (p.(Ala378CysfsTer80)). While this variant, located in exon 9 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 from gnomAD v2.1.1 (PM2_Supporting). This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors). In summary, c.1132_1133del meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PVS1, PM2_supporting.

Met criteria codes

PVS1	✔	While this variant, located in exon 9 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	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.0.0: absent

Not Met criteria codes

PP1	✖	This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors).
PP4	✖	This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors).

Curation History

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