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.166G>C

Version: 1.0

CA367398808

2628365 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 303623b2-a555-499c-a2ad-9a96bfacb6cb
Approved on: 2023/10/3
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HGVS expressions

NM_001354803.2:c.166G>C
NC_000007.14:g.44145618C>G
CM000669.2:g.44145618C>G
NC_000007.13:g.44185217C>G
CM000669.1:g.44185217C>G
NC_000007.12:g.44151742C>G
NG_008847.1:g.48806G>C
NG_008847.2:g.57553G>C
ENST00000395796.8:c.*1130G>C
ENST00000616242.5:c.*252G>C
ENST00000683378.1:n.358G>C
ENST00000336642.9:c.166G>C
ENST00000345378.7:c.1135G>C
ENST00000403799.8:c.1132G>C
ENST00000671824.1:c.1195G>C
ENST00000672743.1:n.144G>C
ENST00000673284.1:c.1132G>C
ENST00000336642.8:c.184G>C
ENST00000345378.6:c.1135G>C
ENST00000395796.7:c.1129G>C
ENST00000403799.7:c.1132G>C
ENST00000437084.1:c.1081G>C
ENST00000459642.1:n.512G>C
ENST00000616242.4:c.1129G>C
NM_000162.3:c.1132G>C
NM_033507.1:c.1135G>C
NM_033508.1:c.1129G>C
NM_000162.4:c.1132G>C
NM_001354800.1:c.1132G>C
NM_001354801.1:c.121G>C
NM_001354802.1:c.-9G>C
NM_001354803.1:c.166G>C
NM_033507.2:c.1135G>C
NM_033508.2:c.1129G>C
NM_000162.5:c.1132G>C
NM_033507.3:c.1135G>C
NM_033508.3:c.1129G>C

Likely Pathogenic

Met criteria codes 4

PP2 PP3 PM5_Strong PM2_Supporting

Not Met criteria codes 4

PS4 PP1 PP4 PM1

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.1132G>C variant in the glucokinase gene, GCK, causes an amino acid change of alanine to proline at codon 378 (p.(Ala378Pro)) of NM_000162.5. This variant failed quality control check in gnomAD 2.1.1; however, there is only 1 filtered allele present (≤ 1 copy in any subpopulation), thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting) GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.9399, which is greater than the MDEP VCEP threshold of 0.70 (PP3). The c.1133C>T, p.(Ala378Val) and c.1132G>A, p.(Ala378Thr) variants have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong). This variant was identified in two unrelated individuals with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold (PMIDs: 22035297, 24918535, internal lab contributor). One of these individuals had HbA1c 5.6 - 7.6%; however, the fasting glucose exceeded mmol/L, and PP4 could not be applied, and there was insufficient clinical data provided for the other individual to evaluate for PP4 (PMIDs: 22035297, 24918535; internal lab contributor). This variant segregated with diabetes with one informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 22035297). In summary, c.1132G>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PM2_Supporting, PP2, PP3, PM5_Strong.

Met criteria codes

PP2	✔	GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.9399, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM5_Strong	✔	The c.1133C>T, p.(Ala378Val) and c.1132G>A, p.(Ala378Thr) variants have been interpreted as pathogenic by the ClinGen MDEP (PM5_Strong).
PM2_Supporting	✔	This variant failed quality control check in gnomAD 2.1.1; however, there is only 1 filtered allele present (≤ 1 copy in any subpopulation), thereby meeting the ClinGen MDEP criteria for PM2_Supporting (PM2_Supporting)

Not Met criteria codes

PS4	✖	This variant was identified in two unrelated individuals with a clinical picture consistent with monogenic diabetes, however PS4_Moderate cannot be applied because this number is below the MDEP threshold (PMID 22035297 and PMID 24918535).
PP1	✖	This variant segregated with diabetes with one informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMIDs: 27236918, 22035297).
PP4	✖	This variant was identified in an individual with HbA1c 5.6 - 7.6%; however, the fasting glucose exceeded mmol/L, and PP4 could not be applied (nternal lab contributors).
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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