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Variant: NM_001354803.2:c.182C>A

Version: 1.2

CA4239423

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: d5362e38-f996-4ef0-b41b-c6bbcdbfb2b5
Approved on: 2024/12/2
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HGVS expressions

NM_001354803.2:c.182C>A
NC_000007.14:g.44145602G>T
CM000669.2:g.44145602G>T
NC_000007.13:g.44185201G>T
CM000669.1:g.44185201G>T
NC_000007.12:g.44151726G>T
NG_008847.1:g.48822C>A
NG_008847.2:g.57569C>A
ENST00000395796.8:c.*1146C>A
ENST00000616242.5:c.*268C>A
ENST00000683378.1:n.374C>A
ENST00000336642.9:c.182C>A
ENST00000345378.7:c.1151C>A
ENST00000403799.8:c.1148C>A
ENST00000671824.1:c.1211C>A
ENST00000672743.1:n.160C>A
ENST00000673284.1:c.1148C>A
ENST00000336642.8:c.200C>A
ENST00000345378.6:c.1151C>A
ENST00000395796.7:c.1145C>A
ENST00000403799.7:c.1148C>A
ENST00000437084.1:c.1097C>A
ENST00000459642.1:n.528C>A
ENST00000616242.4:c.1145C>A
NM_000162.3:c.1148C>A
NM_033507.1:c.1151C>A
NM_033508.1:c.1145C>A
NM_000162.4:c.1148C>A
NM_001354800.1:c.1148C>A
NM_001354801.1:c.137C>A
NM_001354802.1:c.8C>A
NM_001354803.1:c.182C>A
NM_033507.2:c.1151C>A
NM_033508.2:c.1145C>A
NM_000162.5:c.1148C>A
NM_033507.3:c.1151C>A
NM_033508.3:c.1145C>A

Likely Pathogenic

Met criteria codes 2

PVS1 PM2_Supporting

Not Met criteria codes 2

PS4 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.1148C>A variant in the glucokinase gene, GCK, results in a premature termination at codon 383 (p.(Ser383Ter)) of NM_000162.5. This variant, located in biologically-relevant exon 9 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copy in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Grpmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). 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 (PMID: 12955723). This variant was identified in another individual with a phenotype suggestive of GCK-hyperglycemia; however, the clinical parameters were not met for PP4 according to ClinGen MDEP VCEP (PhD dissertation by Ovsyannikova [https://iimed.ru/userfiles/models/passages-files/Ovsyannikova_AK_dissertacia.pdf], variant also cited in PMID: 33477506). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the MDEP threshold (PMIDs: 12955723, 33477506, PhD dissertation by Ovsyannikova). In summary, c.1148C>A 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	✔	This variant, located in biologically-relevant exon 9 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256).
PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to 1 copy in the European non-Finnish subpopulation and 0 copy in any other subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Grpmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). gnomAD v4.0.0: Grpmax Filtering AF = 0; 1 case in ENF

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: 12955723; PhD dissertation by Ovsyannikova).

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 (PMID: 12955723). This variant was identified in another individual with a phenotype suggestive of GCK-hyperglycemia, however the clinical parameters were not met for PP4 according to ClinGen MDEP VCEP (PhD dissertation by Ovsyannikova).

Curation History

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