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_000162.5(GCK):c.660C>A (p.Cys220Ter)

Version: 1.0

CA367401189

1172896 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: a0440cfd-bea7-4669-9015-029cdffa3640
Approved on: 2023-10-13
Published on: 2023-10-13

HGVS expressions

NM_000162.5:c.660C>A
NM_000162.5(GCK):c.660C>A (p.Cys220Ter)
NC_000007.14:g.44149779G>T
CM000669.2:g.44149779G>T
NC_000007.13:g.44189378G>T
CM000669.1:g.44189378G>T
NC_000007.12:g.44155903G>T
NG_008847.1:g.44645C>A
NG_008847.2:g.53392C>A
ENST00000395796.8:c.*658C>A
ENST00000616242.5:c.660C>A
ENST00000682635.1:n.1146C>A
ENST00000345378.7:c.663C>A
ENST00000403799.8:c.660C>A
ENST00000671824.1:c.660C>A
ENST00000673284.1:c.660C>A
ENST00000345378.6:c.663C>A
ENST00000395796.7:c.657C>A
ENST00000403799.7:c.660C>A
ENST00000437084.1:c.609C>A
ENST00000616242.4:c.657C>A
NM_000162.3:c.660C>A
NM_033507.1:c.663C>A
NM_033508.1:c.657C>A
NM_000162.4:c.660C>A
NM_001354800.1:c.660C>A
NM_033507.2:c.663C>A
NM_033508.2:c.657C>A
NM_033507.3:c.663C>A
NM_033508.3:c.657C>A

Pathogenic

Met criteria codes 5

PVS1 | PP1_Strong | PS4 | PP4 | PM2_Supporting

Not Met criteria codes 1

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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.660C>A variant in the glucokinase gene, GCK, results in a premature termination at codon 220 (p.(Cys220Ter)) of NM_000162.5. This variant, located in exon 6 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: 9790256). This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in multiple families (PP1_Strong; internal lab contributors). This variant was identified in at least 11 unrelated individuals with hyperglycemia (PS4; PMIDs: 21348868, 3347750, 31638168, 20337973, 12627330, 16602010, internal lab contributors. This variant was identified in at least 2 individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, c.660C>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0 approved 8/11/2023): PVS1, PP1_Strong, PS4, PP4, PM2_Supporting.

Met criteria codes

PVS1	✔	This variant, located in exon 6 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: 9790256).
PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia, with 5 informative meioses in multiple families (PP1_Strong; internal lab contributors).
PS4	✔	This variant was identified in at least 11 unrelated individuals with hyperglycemia (PS4; PMIDs: 21348868, 3347750, 31638168, 20337973, 12627330, 16602010, internal lab contributors.
PP4	✔	This variant was identified in at least 2 individuals with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (PP4; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

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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