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Variant: NM_000162.5(GCK):c.679+2T>C

Version: 1.0

CA367401107

3768773 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: d5bd8645-769e-4843-86fc-400038206ca3
Approved on: 2025/9/17
Published on: 2025/9/26

HGVS expressions

NM_000162.5:c.679+2T>C
NM_000162.5(GCK):c.679+2T>C
NC_000007.14:g.44149758A>G
CM000669.2:g.44149758A>G
NC_000007.13:g.44189357A>G
CM000669.1:g.44189357A>G
NC_000007.12:g.44155882A>G
NG_008847.1:g.44666T>C
NG_008847.2:g.53413T>C
ENST00000395796.8:c.*677+2T>C
ENST00000616242.5:c.679+2T>C
ENST00000682635.1:n.1167T>C
ENST00000345378.7:c.682+2T>C
ENST00000403799.8:c.679+2T>C
ENST00000671824.1:c.679+2T>C
ENST00000673284.1:c.679+2T>C
ENST00000345378.6:c.682+2T>C
ENST00000395796.7:c.676+2T>C
ENST00000403799.7:c.679+2T>C
ENST00000437084.1:c.628+2T>C
ENST00000616242.4:c.676+2T>C
NM_000162.3:c.679+2T>C
NM_033507.1:c.682+2T>C
NM_033508.1:c.676+2T>C
NM_000162.4:c.679+2T>C
NM_001354800.1:c.679+2T>C
NM_033507.2:c.682+2T>C
NM_033508.2:c.676+2T>C
NM_033507.3:c.682+2T>C
NM_033508.3:c.676+2T>C

Pathogenic

Met criteria codes 6

PM2_Supporting PVS1 PS4_Moderate PP4_Moderate PS1_Supporting PP1_Strong

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 3.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.679+2T>C variant in glucokinase gene, GCK, is predicted to remove a canonical splice donor site in intron 6 of transcript NM_000162.5. This variant is predicted to cause skipping of biologically-relevant exon 6 of 10, resulting in a frameshift, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors). Additionally, one of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6%, antibody negative) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia with four informative meioses in three families (PP1_Strong; internal lab contributors). Another variant within same splice donor ±1,2 dinucleotide, c.679+1G>T, has been classified as pathogenic by the ClinGen MDEP, and both variants have the same predicted impact on splicing by SpliceAI (0.99) (PS1_Supporting). In summary, c.679+2T>C meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.0.0, approved 7/23/2025): PVS1, PP1_Strong, PS4_Moderate, PP4_Moderate, PM2_Supporting, PS1_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1	✔	This variant is predicted to cause skipping of biologically-relevant exon 6 of 10, resulting in a frameshift, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 19790256).
PS4_Moderate	✔	This variant was identified in five unrelated individuals with hyperglycemia (PS4_Moderate; internal lab contributors).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative autoantibodies) (PP4_Moderate; internal lab contributors).
PS1_Supporting	✔	Another variant within same splice donor ±1,2 dinucleotide, c.679+1G>T, has been classified as pathogenic by the ClinGen MDEP, and both variants have the same predicted impact on splicing by SpliceAI (0.99) (PS1_Supporting).
PP1_Strong	✔	This variant segregated with hyperglycemia with four informative meioses in three families (PP1_Strong; internal lab contributors).

Curation History

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