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Variant: NM_000162.5(GCK):c.679G>A (p.Gly227Ser)

Version: 1.0

CA367401117

2136518 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: fde0b5b3-0b72-41a9-8742-2d5a045f6ba0
Approved on: 2025/9/26
Published on: 2025/9/26

HGVS expressions

NM_000162.5(GCK):c.679G>A (p.Gly227Ser)
NM_000162.5:c.679G>A
NC_000007.14:g.44149760C>T
CM000669.2:g.44149760C>T
NC_000007.13:g.44189359C>T
CM000669.1:g.44189359C>T
NC_000007.12:g.44155884C>T
NG_008847.1:g.44664G>A
NG_008847.2:g.53411G>A
ENST00000395796.8:c.*677G>A
ENST00000616242.5:c.679G>A
ENST00000682635.1:n.1165G>A
ENST00000345378.7:c.682G>A
ENST00000403799.8:c.679G>A
ENST00000671824.1:c.679G>A
ENST00000673284.1:c.679G>A
ENST00000345378.6:c.682G>A
ENST00000395796.7:c.676G>A
ENST00000403799.7:c.679G>A
ENST00000437084.1:c.628G>A
ENST00000616242.4:c.676G>A
NM_000162.3:c.679G>A
NM_033507.1:c.682G>A
NM_033508.1:c.676G>A
NM_000162.4:c.679G>A
NM_001354800.1:c.679G>A
NM_033507.2:c.682G>A
NM_033508.2:c.676G>A
NM_033507.3:c.682G>A
NM_033508.3:c.676G>A

Pathogenic

Met criteria codes 5

PS3 PS4 PP3 PM2_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.679G>A variant in the glucokinase gene, GCK, causes an amino acid change of glycine to serine at codon 227 (p.(Gly227Ser)) of NM_000162.5. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant was identified in nine individuals with hyperglycemia (PS4; PMID: 37838154; internal lab contributors). This variant segregated with hyperglycemia with at least five meioses in five families (PP1_Strong; internal lab contributors). The computational splicing predictor SpliceAI gives a score of 0.63 for donor loss, predicting that the variant disrupts the donor site of intron 6 (PP3). Furthermore, there is evidence from RNA studies that this variant results in aberrant splicing with minigene assay showing a complex alteration of residual full-length transcripts and 2 alternative transcripts (deletion of the last 4 bp of exon 6 (r.676_679del, p.Val226Alafs*67) and deletion of the last 16 bp of exon 6 (r.663_679del, p.Val222Alafs*67) (PS3; PMID 40225161). In summary, c.679G>A 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): PS3, PS4, PP1_Strong, PM2_Supporting, PP3.

Met criteria codes

PS3	✔	There is evidence from RNA and in silico studies that this non-canonical splicing variant results in aberrant splicing with minigene assay showing a complex alteration with residual full-length transcripts and 2 alternative transcripts (deletion of the last 4 bp of exon 6 (r.676_679del, p.Val226Alafs*67) and deletion of the last 16 bp of exon 6 (r.663_679del, p.Val222Alafs*67) (PS3; PMID 40225161).
PS4	✔	This variant was identified in nine individuals with hyperglycemia (PS4; PMID: 37838154; internal lab contributors).
PP3	✔	The computational splicing predictor SpliceAI gives a score of 0.63 for donor loss, predicting that the variant disrupts the donor site of intron 6 (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP1_Strong	✔	This variant segregated with hyperglycemia with at least five meioses in five families (PP1_Strong; internal lab contributors).

Curation History

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