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Variant: NM_000162.5(GCK):c.579+4del

Version: 1.0

CA2573051051

2431839 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: a82dfcfb-8b49-4ab7-b1ed-ab9a54e4e373
Approved on: 2024/4/19
Published on: 2024/4/19

HGVS expressions

NM_000162.5(GCK):c.579+4del
NM_000162.5:c.579+4del
NC_000007.14:g.44149965del
CM000669.2:g.44149965del
NC_000007.13:g.44189564del
CM000669.1:g.44189564del
NC_000007.12:g.44156089del
NG_008847.1:g.44459del
NG_008847.2:g.53206del
ENST00000395796.8:c.*577+4del
ENST00000616242.5:c.579+4del
ENST00000682635.1:n.1065+4del
ENST00000345378.7:c.582+4del
ENST00000403799.8:c.579+4del
ENST00000671824.1:c.579+4del
ENST00000673284.1:c.579+4del
ENST00000345378.6:c.582+4del
ENST00000395796.7:c.576+4del
ENST00000403799.7:c.579+4del
ENST00000437084.1:c.528+4del
ENST00000616242.4:c.576+4del
NM_000162.3:c.579+4del
NM_033507.1:c.582+4del
NM_033508.1:c.576+4del
NM_000162.4:c.579+4del
NM_001354800.1:c.579+4del
NM_033507.2:c.582+4del
NM_033508.2:c.576+4del
NM_033507.3:c.582+4del
NM_033508.3:c.576+4del

Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4_Moderate PS3 PP1_Moderate

Not Met criteria codes 1

PS4

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.579+4del variant in the glucokinase gene, GCK, is predicted to remove a canonical splice donor site in intron 5 of NM_000162.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational splicing predictor SpliceAI gives a score of 0.92 for donor loss, predicting that the variant disrupts the donor site of intron 5 of GCK (PP3). There is evidence from RNA studies that this non-canonical splicing variant results in aberrant splicing, indicating that this variant impacts protein function (ClinVar Accession: SCV004037045.1) (PS3). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and antibody negative) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes, with three informative meioses in two families with MODY (PP1_Moderate; internal lab contributors). This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). In summary, c.605T>G 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): PS3, PM2_Supporting, PP3, PP1_Moderate, PP4_Moderate.

Met criteria codes

PM2_Supporting ✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP3 ✔	The computational splicing predictor SpliceAI gives a score of 0.92 for donor loss, predicting that the variant disrupts the donor site of intron 5 of GCK (PP3).
PP4_Moderate ✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors).
PS3 ✔	There is evidence from RNA studies that this non-canonical splicing variant results in aberrant splicing, indicating that this variant impacts protein function (ClinVar Accession: SCV004037045.1)(PS3).
PP1_Moderate ✔	This variant segregated with diabetes, with three informative meioses in two families with MODY (PP1_Moderate; internal lab contributors).

Not Met criteria codes

PS4 ✖	

This variant was identified in two unrelated individuals with hyperglycemia; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).

Curation History

Showing 1 to 1 of 1 rows

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