

Supplementary Data:

Table S1: List of primers used in this report.

Sample	Forward Primer	Reverse Primer
<b>DNA Sanger Sequencing</b>		
<b>Patient 1</b>	AGCCAAAGTACTTTTTCAACAAACT	AGAGACTGAAGGATGGCTCG
<b>Patient 2</b>	TCCCCACCTTGATCTCACTC	CAAACATCCCACTCATTCCA
<b>cDNA Sanger sequencing</b>		
<b>Patient 1</b>	1. ATCGGTGAAATTGCTCCAACCG 2. TTTTCATCAGCTGGCCATCG	1. GGTATCTGGGGCTTTCTGGAC 2. AGAGACTGAAGGATGGCTCG
<b>qRT-PCR</b>		
<b>GAPDH</b>	CTGACTTCAACAGCGACACC	TTACTCCTTGGAGGCCATGT
<b>GLUT1</b>	TGTCGTGTCGCTGTTTGTG	ATGGCCACGATGCTCAGATA
<b>GLUT3</b>	AGCTCTCTGGGATCAATGCT	GAGTCCTTCTTCCTGCCCTT

Table S2: List of 123 miRNA specific to the case 1

hsa-let-7e-5p	hsa-miR-331-3p	hsa-miR-552-3p
hsa-miR-1-5p	hsa-miR-342-3p	hsa-miR-554
hsa-miR-103a-3p	hsa-miR-342-5p	hsa-miR-561-3p
hsa-miR-107	hsa-miR-365b-5p	hsa-miR-562
hsa-miR-1183	hsa-miR-371b-5p	hsa-miR-564
hsa-miR-1202	hsa-miR-381-3p	hsa-miR-566
hsa-miR-1204	hsa-miR-425-5p	hsa-miR-567
hsa-miR-1228-3p	hsa-miR-433-3p	hsa-miR-571
hsa-miR-1246	hsa-miR-450a-5p	hsa-miR-573
hsa-miR-1248	hsa-miR-451a	hsa-miR-577
hsa-miR-1249-5p	hsa-miR-486-3p	hsa-miR-579-3p
hsa-miR-1250-5p	hsa-miR-499a-3p	hsa-miR-580-3p
hsa-miR-1258	hsa-miR-5001-3p	hsa-miR-589-5p
hsa-miR-125a-5p	hsa-miR-503-5p	hsa-miR-595
hsa-miR-125b-5p	hsa-miR-506-3p	hsa-miR-599
hsa-miR-1277-3p	hsa-miR-509-5p	hsa-miR-604
hsa-miR-1285-3p	hsa-miR-516b-5p	hsa-miR-605-5p
hsa-miR-129-5p	hsa-miR-517b-3p	hsa-miR-610
hsa-miR-1296-5p	hsa-miR-518b	hsa-miR-614
hsa-miR-1304-3p	hsa-miR-518d-3p	hsa-miR-615-5p
hsa-miR-1306-5p	hsa-miR-5196-3p+hsa-miR-6732-3p	hsa-miR-617

hsa-miR-1322	hsa-miR-519b-5p+hsa-miR-519c-5p+hsa-miR-523-5p+hsa-miR-518e-5p+hsa-miR-522-5p+hsa-miR-519a-5p	hsa-miR-619-3p
hsa-miR-143-3p	hsa-miR-520a-3p	hsa-miR-624-3p
hsa-miR-144-3p	hsa-miR-520a-5p	hsa-miR-637
hsa-miR-148a-3p	hsa-miR-520b	hsa-miR-638
hsa-miR-148b-3p	hsa-miR-520c-3p	hsa-miR-641
hsa-miR-154-5p	hsa-miR-520e	hsa-miR-642a-3p
hsa-miR-181b-2-3p	hsa-miR-520f-3p	hsa-miR-649
hsa-miR-182-5p	hsa-miR-521	hsa-miR-6511a-5p
hsa-miR-18a-5p	hsa-miR-523-3p	hsa-miR-654-3p
hsa-miR-1908-3p	hsa-miR-524-3p	hsa-miR-656-3p
hsa-miR-196a-3p	hsa-miR-539-3p	hsa-miR-661
hsa-miR-199a-3p+hsa-miR-199b-3p	hsa-miR-539-5p	hsa-miR-663a
hsa-miR-19b-3p	hsa-miR-541-3p	hsa-miR-664b-3p
hsa-miR-20a-5p+hsa-miR-20b-5p	hsa-miR-544a	hsa-miR-769-5p
hsa-miR-221-5p	hsa-miR-545-3p	hsa-miR-93-5p
hsa-miR-23c	hsa-miR-548ad-3p	hsa-miR-99b-5p
hsa-miR-24-3p	hsa-miR-548al	
hsa-miR-25-3p	hsa-miR-548b-3p	

hsa-miR-29a-3p	hsa-miR-548c-5p+hsa-miR-548o-5p+hsa-miR-548am-5p	
hsa-miR-30d-5p	hsa-miR-548h-5p	
hsa-miR-3158-3p	hsa-miR-548l	
hsa-miR-324-5p	hsa-miR-550a-5p	

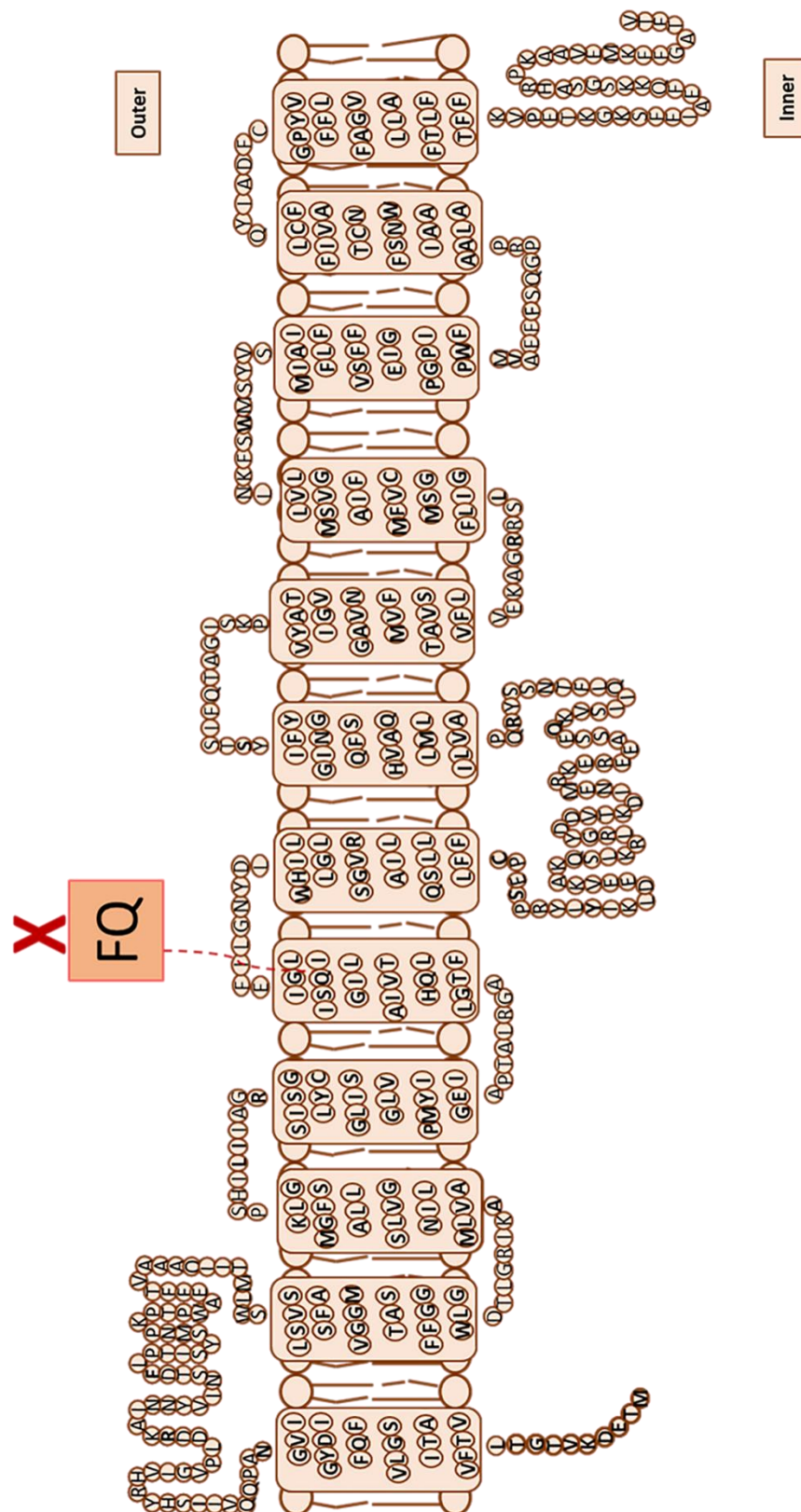


Figure S1: Expected effect of the intronic mutation on GLUT2 topology (no loss or gain of amino acids).

2 variants found

Download Results

Sort By: Chrom/Pos Asc

SLC2A2

GTEx

gnomAD

Gene Search

chr3:170723901

A>C

splice region variant

HGVSc: c.613-7T>G

google | pubmed

CADD PHRED 11.47

DANN SCORE 0.42

EIGEN PHRED 12

SPICE AI 0.97

THIS CALLSET 0.0033

AC=2 out of 2

SKG WGS 0.0

EXAC 0.0 Hom=0

GNOMAD EXOMES 0.0 Hom=0

GNOMAD GENOMES 0.0 Hom=0

QDB-BL-0000-FAMS2-P-2-1,0200212091

C / C

##

Note

Tags

SLC2A2

GTEx

gnomAD

Gene Search

chr3:170743629

T>G

intron variant

HGVSc: c.15+816A>C

google | pubmed

CADD PHRED 5.788

DANN SCORE 0.75

EIGEN PHRED 4.3

THIS CALLSET 0.0033

AC=2 out of 2

SKG WGS 0.0

EXAC 0.0 Hom=0

GNOMAD EXOMES 0.0 Hom=0

GNOMAD GENOMES 0.0 Hom=0

QDB-BL-0000-FAMS2-P-2-1,0200212091

G / G

is

Note

Tags

Figure S2: Two variants in *SLC2A2* were found in SeqR. Whole genome sequencing data for case 1 was uploaded in SeqR and two variants (one pathogenic and other likely benign) were detected.

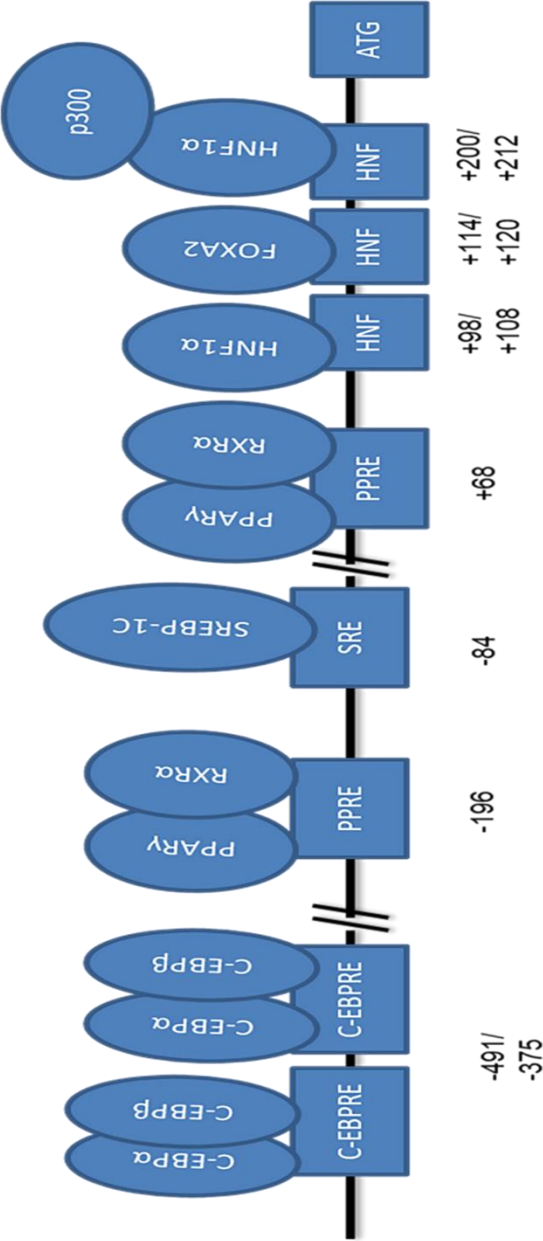


Figure S3: Genes reported to regulate the expression of GLUT2. 60 genes, most of the transcription factors, were found in the literature to regulate the expression of GLUT2 (summarized in upper panel). The relative binding sites within the GLUT2 promoter of a select number of these transcription factors are illustrated in the lower panel.



## Gating Strategy

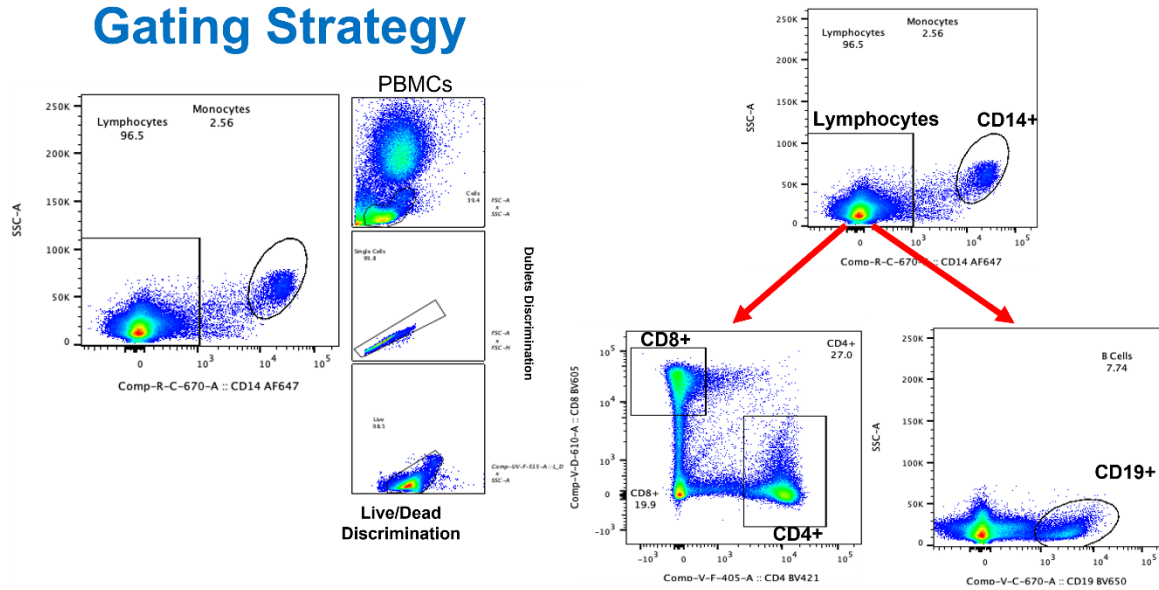
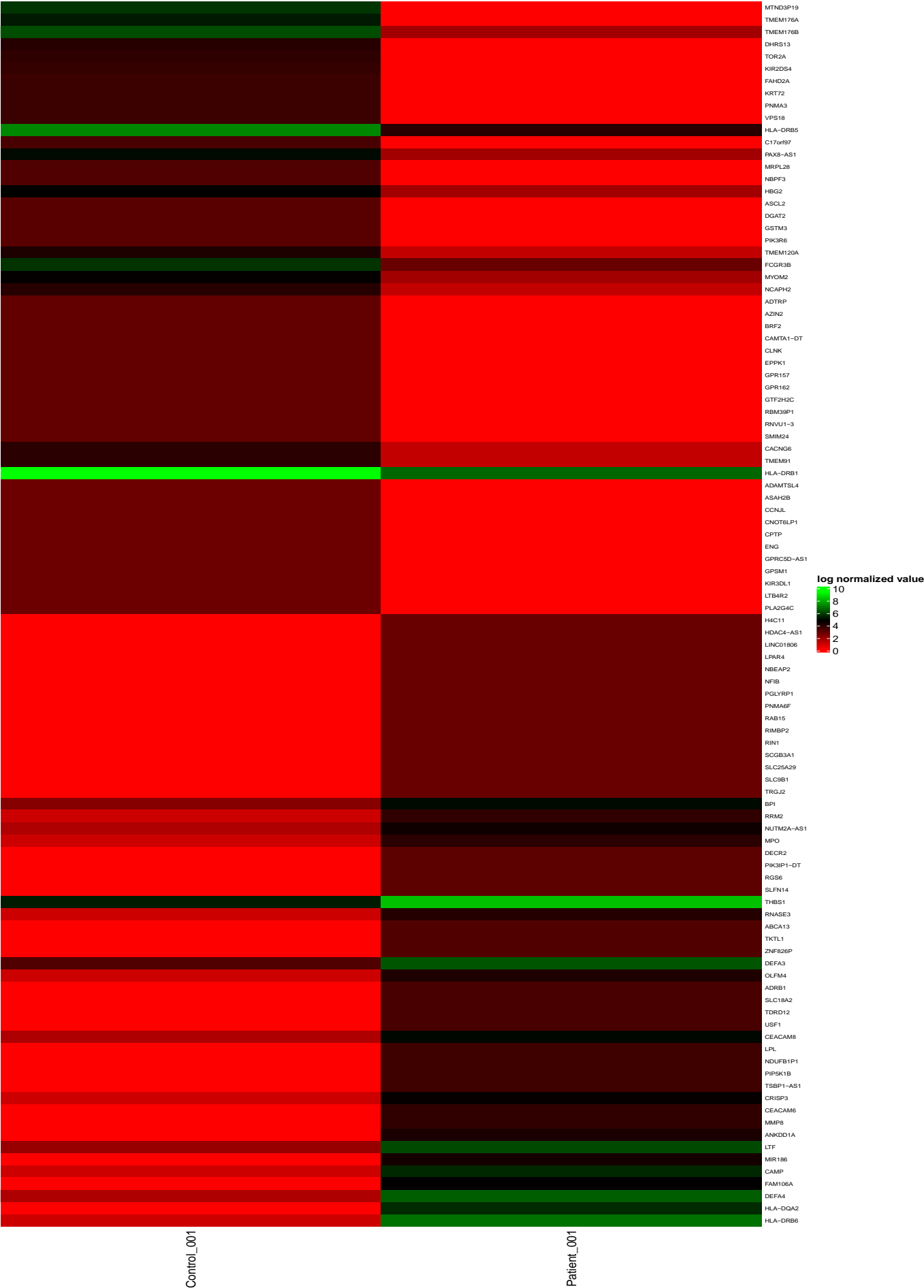


Figure S5: Flow cytometry to assess GLUT2 expression in each cell type in healthy PBMCs. Illustration of the gating strategy used. T Lymphocytes (CD4+, CD8+), B lymphocytes (CD19+), monocytes (CD14+) extracted from a healthy control and the individual cells were sorted using the gate strategy.

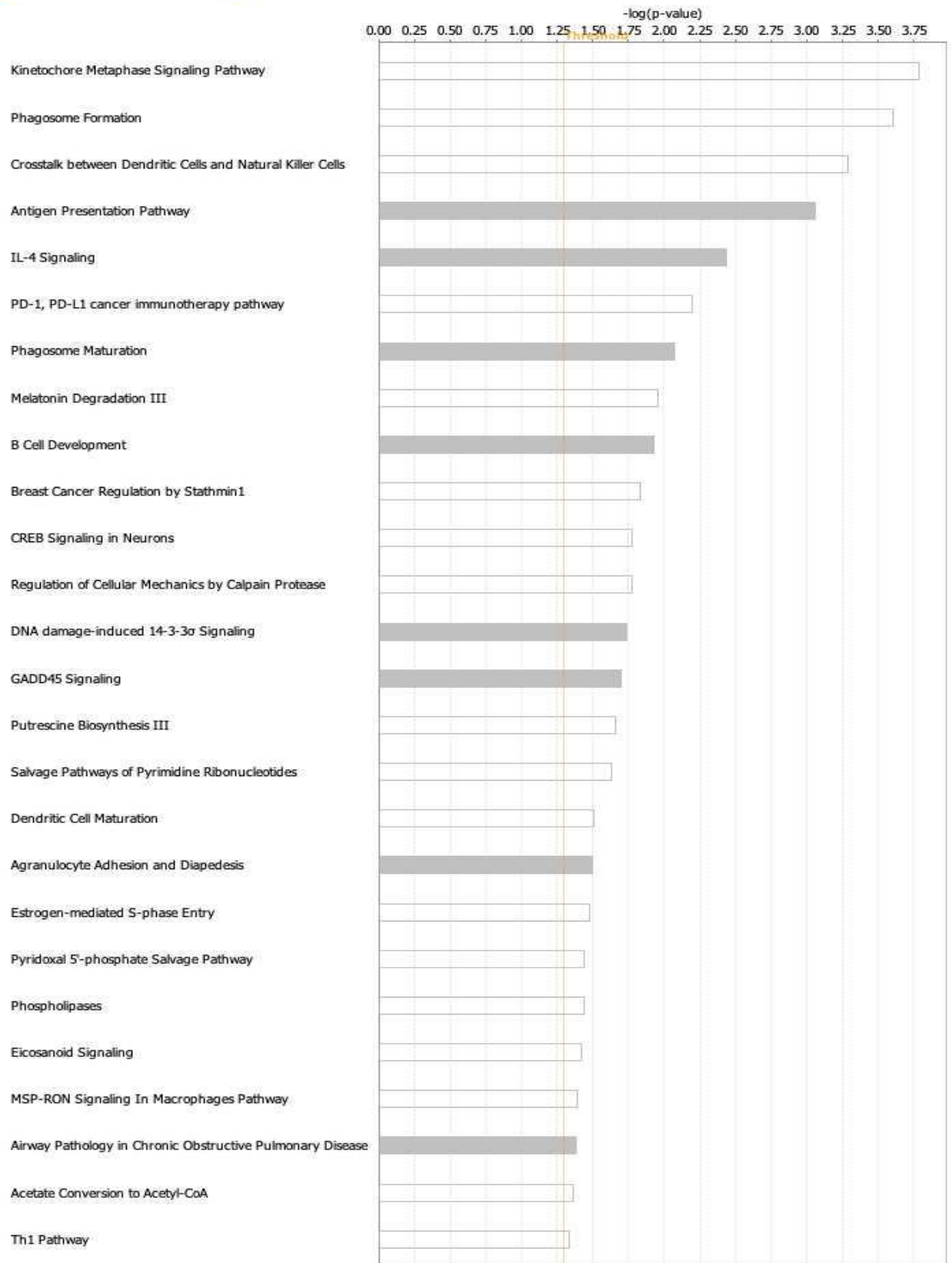
a)



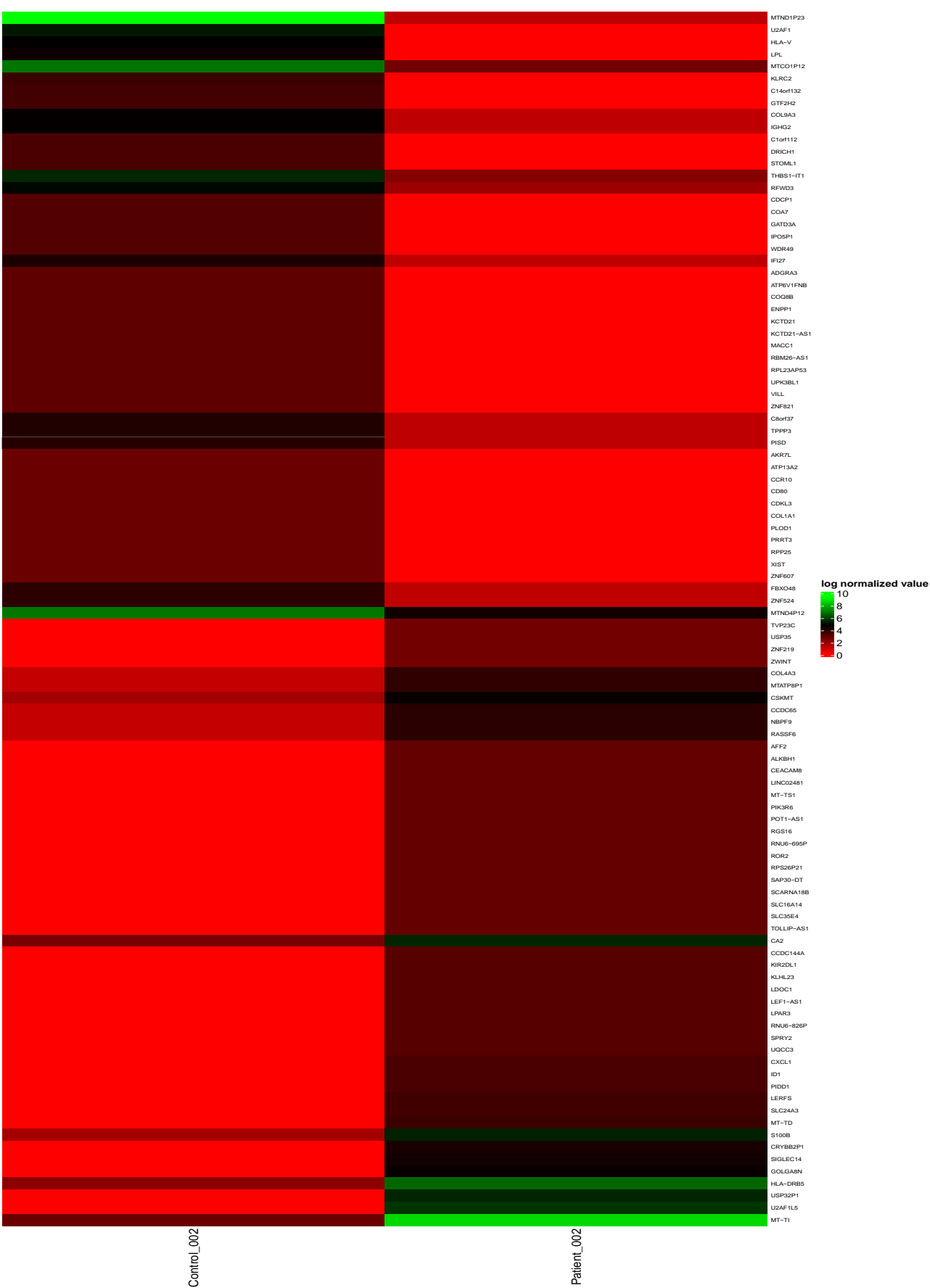
b)

Analysis: C1\_vs\_P1\_less\_and\_greaterthan\_logFC\_2 - 2021-09-23 06:38 PM

■ positive z-score □ z-score = 0 ■ negative z-score ■ no activity pattern available



c)



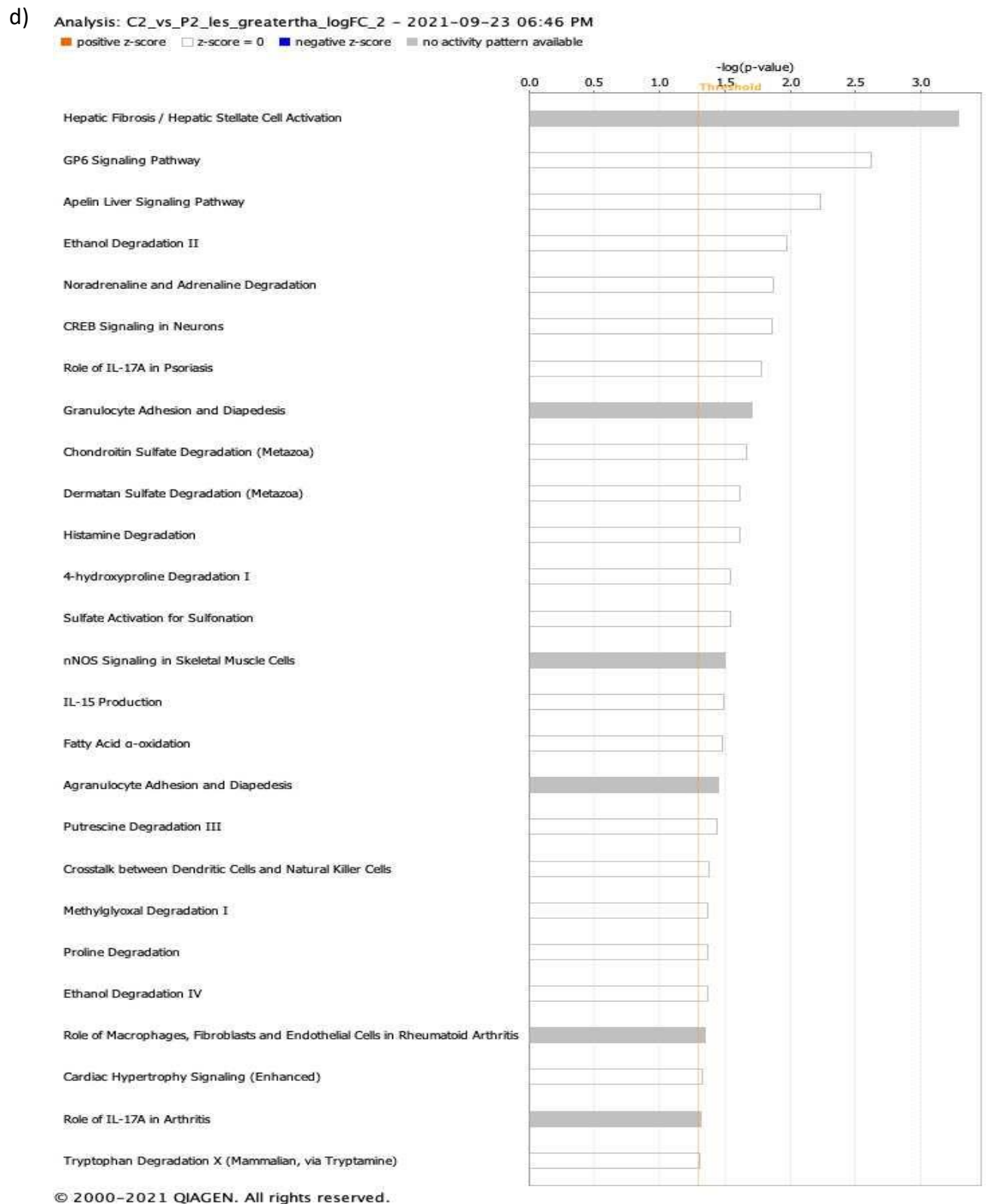


Figure S6: RNA-Seq analysis for patients and their controls. (a & c) Patients 1 and 2 had differentially regulated genes not associated with dysglycemia except for two genes (RETN (resistin) in patient-1 (found in >500 genes differentially regulated list) and ENPP1 in patient-

2) involved in insulin resistance. (b & d) Pathways other than dysglycemia might be dysregulated in patients 1 and 2 in comparison to controls.



strongest correlation. Patient and healthy control showed a strong correlation. (b) a box plot is overlaid on a violin plot to display the distribution of the log of the un-normalized gene counts for each sample. Patient and healthy control showed a more similar data distribution.

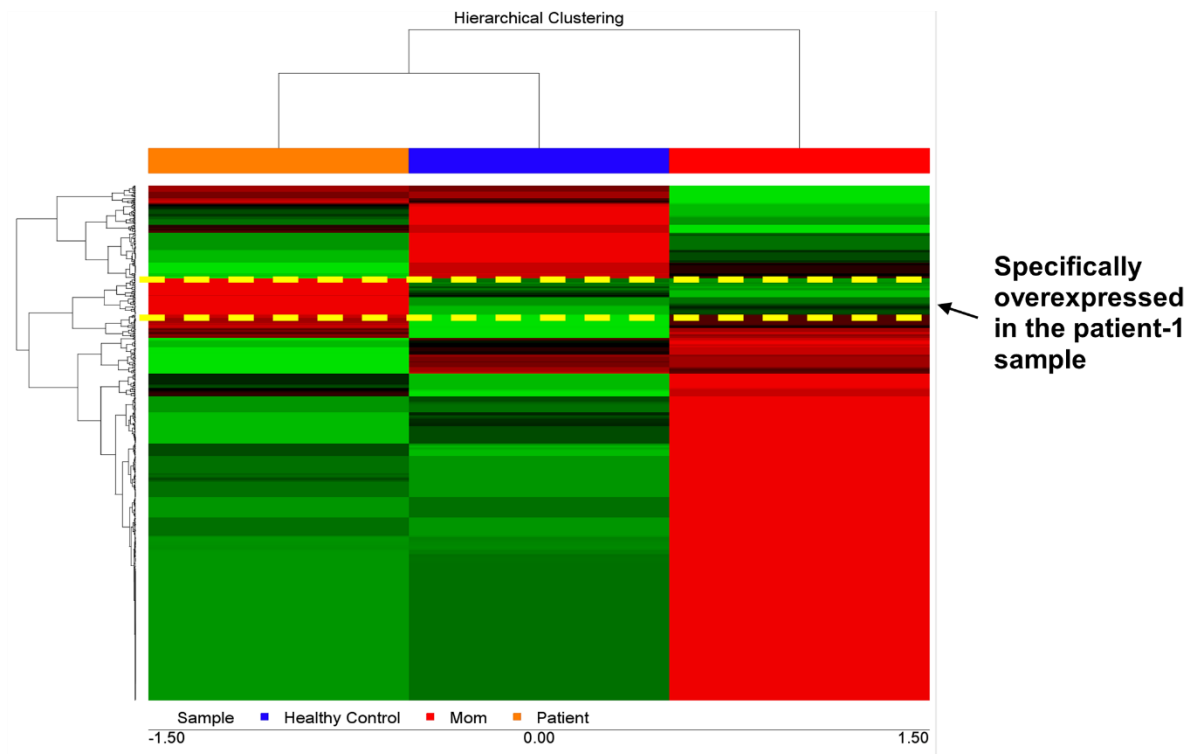


Figure S8. Heat map generated by Partek for case 1. 123 miRNAs were specific to the patient-1, with 118 mapped following IPA analysis. The region marked with the yellow dotted line includes miRNAs specially overexpressed in the patient.

### ▼ Diseases and Disorders

Name	p-value range	# Molecules
Organismal Injury and Abnormalities	4.93E-02 - 1.25E-34	61
Reproductive System Disease	3.72E-02 - 1.25E-34	38
Inflammatory Disease	1.40E-02 - 2.96E-22	28
Inflammatory Response	2.80E-02 - 2.96E-22	26
Renal and Urological Disease	4.56E-03 - 2.96E-22	19

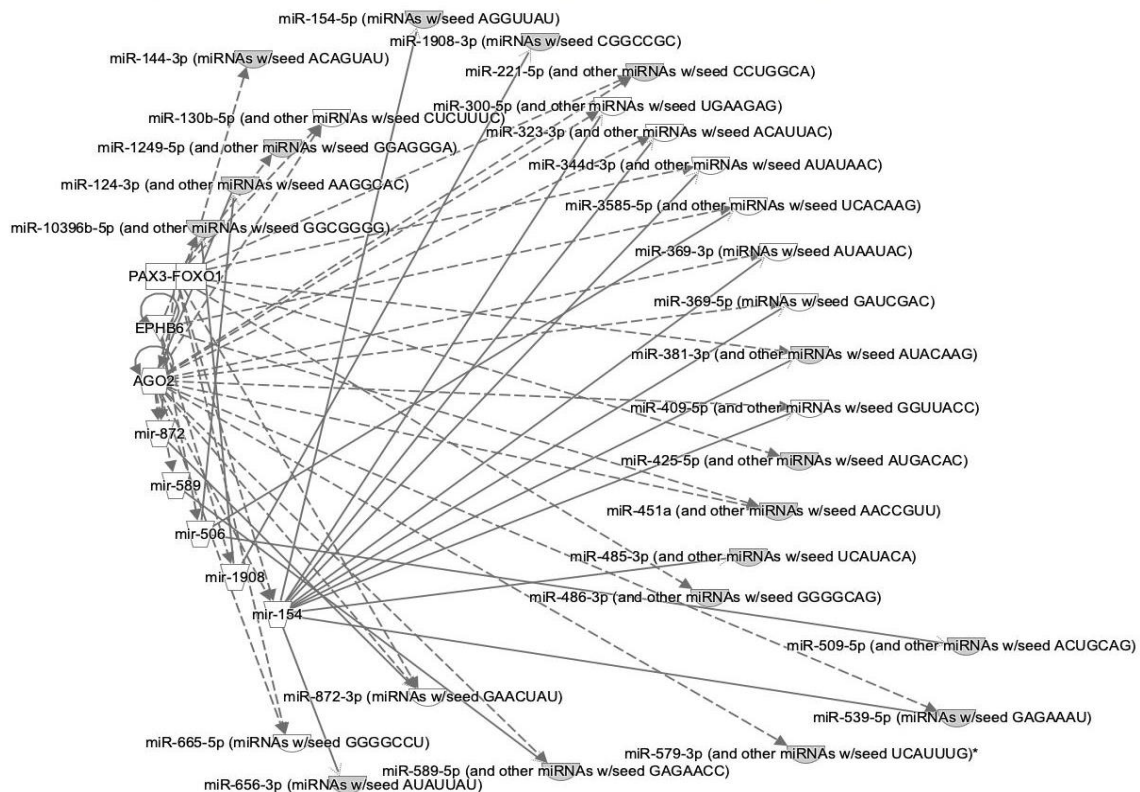
### ▼ Molecular and Cellular Functions

Name	p-value range	# Molecules
Cellular Development	4.32E-02 - 3.74E-08	31
Cellular Growth and Proliferation	4.32E-02 - 3.74E-08	32
Cell Cycle	4.62E-02 - 4.43E-05	10
Cellular Movement	3.93E-02 - 8.31E-05	18
Free Radical Scavenging	1.14E-03 - 1.14E-03	2

### ▼ Physiological System Development and Function

Name	p-value range	# Molecules
Organismal Development	4.98E-02 - 7.68E-11	17
Embryonic Development	4.32E-02 - 4.43E-05	4
Cardiovascular System Development and Function	2.46E-02 - 8.61E-05	11
Organ Morphology	1.88E-02 - 8.61E-05	9
Hematological System Development and Function	4.32E-02 - 9.73E-05	9

## Network 1:



## Network 2:

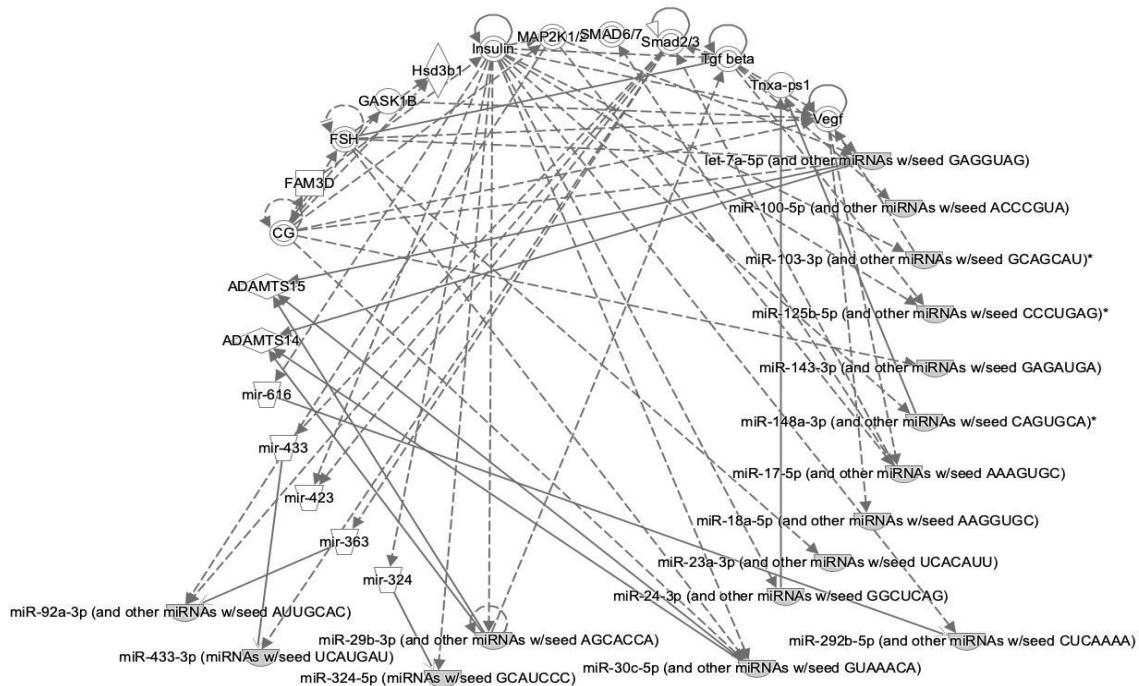


Figure S9: Ingenuity Pathway (IPA) functional analysis to generate networks of diseases and disorders associated with miRNAs. Two networks with the highest scores are illustrated. Network 1 (score:33) included functions associated with organismal injury and abnormalities, skeletal and muscular system development and function, and tissue morphology, and associated with AGO2, EPHB6, PAX3-FOXO1. Network 2 (score: 31) included glomerular injury, Inflammatory disease, and inflammatory response, and was associated with ADAMTS14, ADAMTS15, CG,

FAM3D, FSH, GASK1B, Hsd3b1, INSULIN, MAP2K1, SMAD6/7, TGF-beta, Tmxa-ps1, and VEGF.

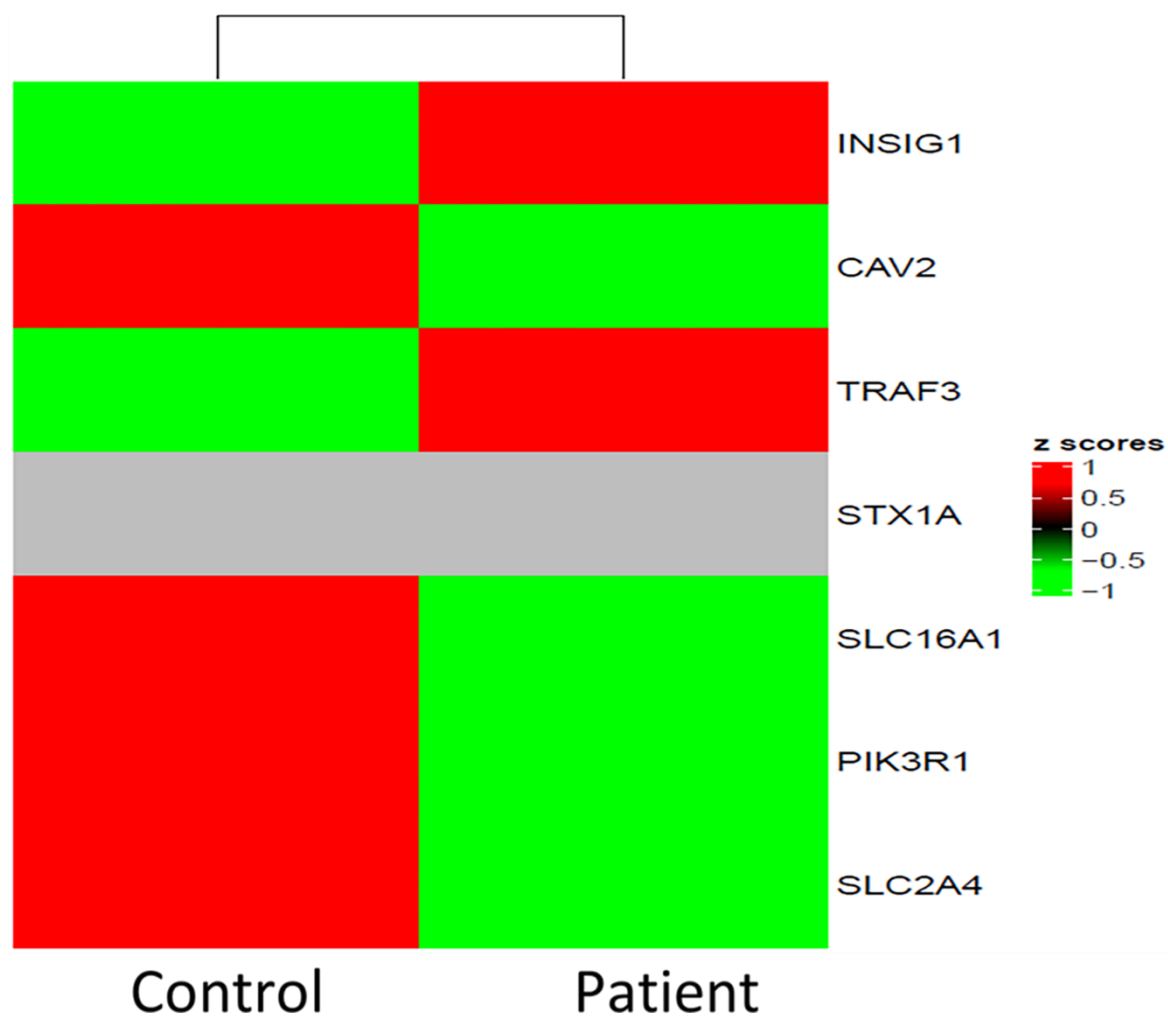
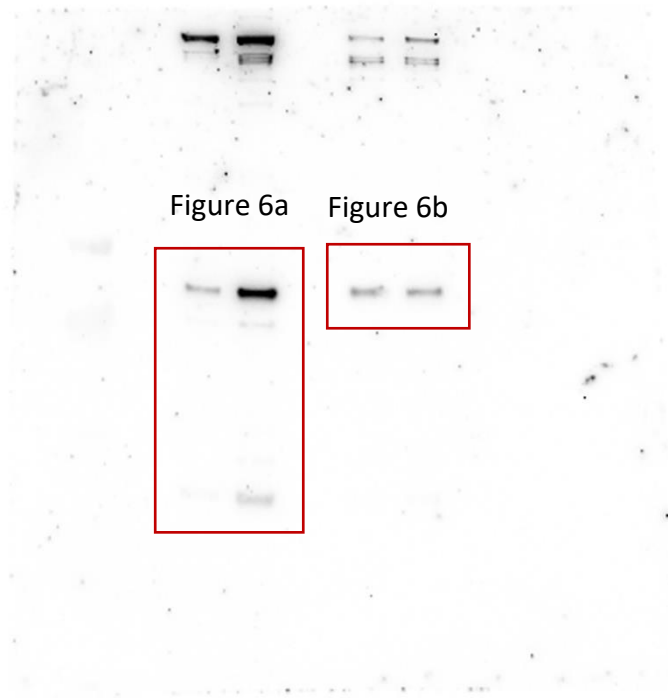
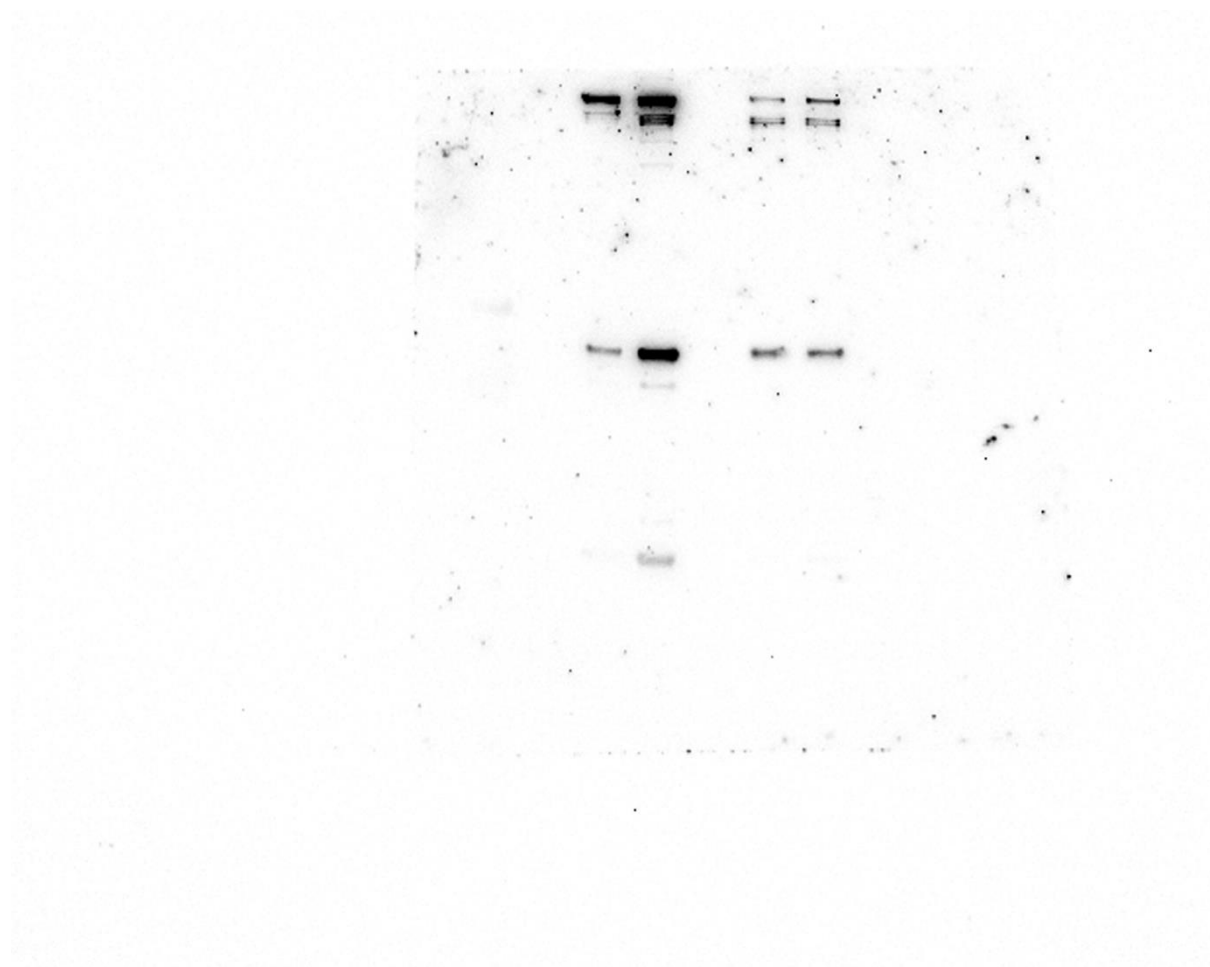


Figure S10: miR-29a-3b overexpression in the patient carrying the intronic GLUT2 mutation coincides with the downregulation of genes involved in insulin production and secretion. CAV2, SLC16A1, PIK3R1, and SLC2A4 were found to be downregulated in the patient in comparison to the healthy control.

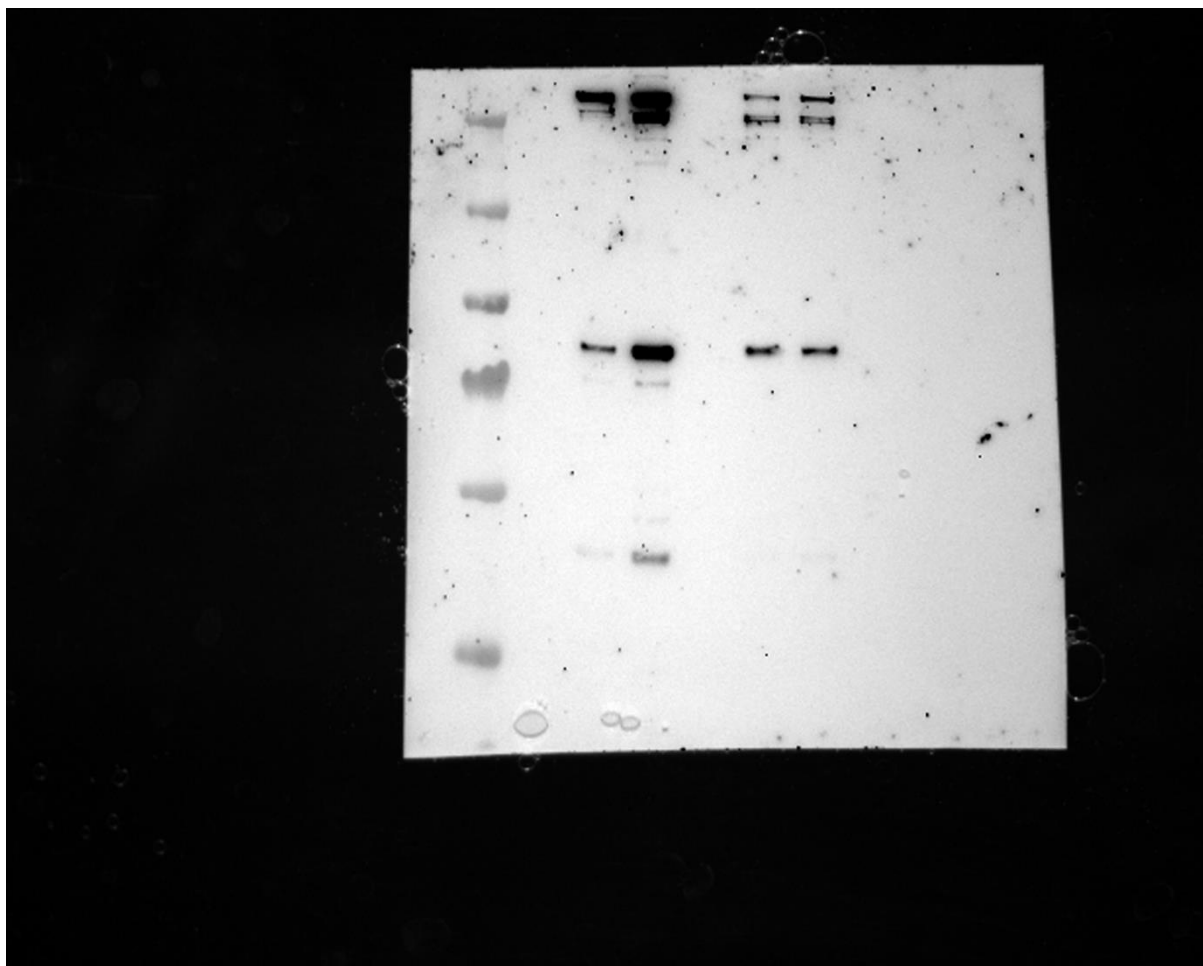
a-1)



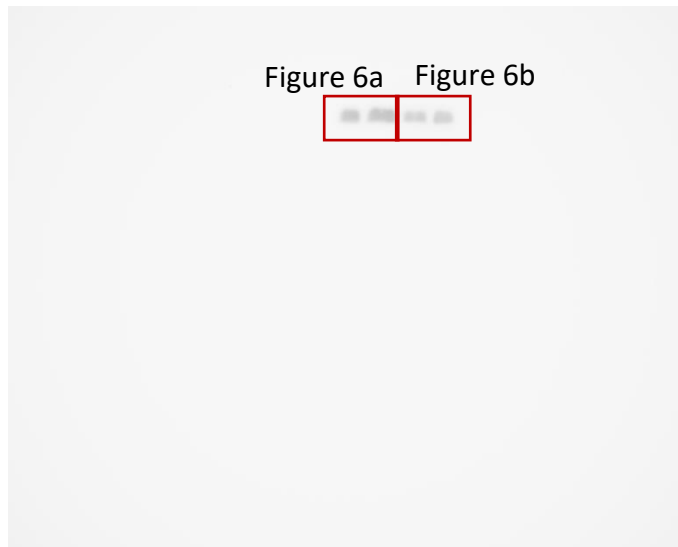
a-2)



a-3)



b-1)



b-2)



Figure S11: Full-length images of western blots (Figure 6). a 1-3 are multiple exposures using the GLUT2 antibody. b 1-2 are multiple exposures using beta-actin antibodies. The red parts in a.1 and b.1 are the cropped parts shown in Figure 6.