Table S1. Description of Gene Expression Omnibus data sets of T2DM and Healthy Controls.

GEO accession ID	T2DM[a]			Control			Platform	Country	Year
	n	Sex (M/F)	Mean age (years)	n	Sex (M/F)	Mean age (years)			
GSE156993	6	3/3	54	6	2/4	41.16	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Brazil	2020
GSE9006	12	6/6	13.41	20	7/13	11.65	Affymetrix Human Genome U133B Array	United States	2007
GSE21321 (GLP6883)	9	9/0		8	9/0		Illumina HumanRef-8 v3.0 expression beadchip	Singapore	2010

The 'a' represents Type 2 Diabetes Mellitus, which is an expansion of the abbreviation 'T2DM'.

Table S2. Description of selection criteria for sorting of Gene Expression Omnibus data sets of T2DM and Healthy Controls.

Parameters	Inclusion criteria	Exclusion criteria
Organism:	Human (Homo sapiens)	Mus musculus, Rattus norvegicus, Xenopus laevis
Data entry types:	Datasets	Series, Samples, Platforms
Study Type:	Expression profiling by array	• Expression profiling by MPSS/RT-PCR/SAGE/SNP array/genome tiling array/high throughput sequencing; • Genome binding/occupancy profiling by SNP array/array/genome tiling array/high throughput sequencing; • Genome variation profiling by SNP array/ array/ genome tiling array/ high throughput sequencing
Sample:	Blood and PBMC	Tissue, Serum, Semen, Saliva, Urine, Body Fluid
Disorders	T2DM compared to non-diabetics	Type 1 Diabetes, Gestational Diabetes, Prediabetes with non-diabetic

Table S3. Description of MicroRNA Expression Omnibus data sets of T2DM and Healthy Controls.

GEO accession ID	T2DM[a]			Control			Platform	Country	Year
	n	Sex (M/F)	Mean age (years)	n	Sex (M/F)	Mean age (years)			
GSE51674	6	4/2	59.33	4	3/1	38	Human miRNA Microarray v14 Rev.2	Italy	2019
GSE21321	9	9/0	-	10	10/0	-	Illumina HumanRef-8 v3.0 expression beadchip	Singapore	2010

The 'a' represents Type 2 Diabetes Mellitus, which is an expansion of the abbreviation 'T2DM'.

Table S4. Description of selection criteria for sorting of MicroRNA Expression Omnibus data sets of T2DM and Healthy Controls.

Parameters	Inclusion criteria	Exclusion criteria
Organism:	Human (Homo sapiens)	Mus musculus, Rattus norvegicus, Arabidopsis thaliana, Danio rerio
Data entry types:	Datasets	Series, Samples, Platforms
Study Type:	Expression profiling by array	• Expression profiling by MPSS/RT-PCR/SAGE/SNP array/genome tiling array/high throughput sequencing; • Genome binding/occupancy profiling by SNP array/array/genome tiling array/high throughput sequencing; • Genome variation profiling by SNP array/ array/ genome tiling array/ high throughput sequencing
Sample:	Tissue, Blood and PBMC	Semen, Saliva, Urine, Body Fluid
Disorders	T2DM compared to non-diabetics	Type 1 Diabetes, Gestational Diabetes, Prediabetes with non-diabetic

Table S5. ANOVA test for clinical, biochemical and gene and microRNA expression profiles for T2DM patients, DN patients and healthy control subjects.

Descriptive	Healthy Control (n=36)	T2DM (n=38)	Diabetic Nephropathy (n=35)	F	Sig.
Age (Years)	31.25 ± 6.31	49.11 ± 6.43	61.57 ± 10.52	130.98	**0.00**
Body Mass Index	24.59 ± 1.89	27.47 ± 3.65	26.07 ± 5.70	2.76	0.07
Waist–hip Ratio	0.90 ± 0.04	0.96 ± 0.07	0.95 ± 0.07	4.39	**0.02**
HbA1c (%)	5.20 ± 0.26	9.42 ± 2.22	8.09 ± 1.72	43.69	**0.00**
Fasting Blood Sugar	95.59 ± 8.25	203.28 ± 81.79	180.45 ± 48.67	35.60	**0.00**
HOMA-IR	2.89 ± 2.31	8.09 ± 9.36	11.82 ± 13.73	7.25	**0.00**
Cholesterol	167.56 ± 36.93	187.69 ± 43.24	178.91 ± 62.94	1.55	0.22
Triglycerides	122.75 ± 44.4	174.14 ± 91.8	172.35 ± 86.6	4.97	**0.00**
Low-density lipoprotein	94.69 ± 38.9	114.75 ± 35.5	109.65 ± 53.40	2.05	**0.13**
High-density lipoprotein	43.11 ± 12.1	40.42 ± 9.0	43.91 ± 11.0	0.99	**0.37**
Urea	23.11 ± 6.70	26.07 ± 10.76	80.34 ± 35.84	69.32	**0.00**
Creatinine	0.90 ± 0.18	0.75 ± 0.19	2.74 ± 1.90	33.19	**0.00**
Insulin (mlU/L)	12.30 ± 9.36	15.71 ± 17.17	28.18 ± 29.15	5.91	**0.00**
GFR (mL/min per 1.73 m^2)	99.26 ± 34.94	117.45 ± 37.74	35.93 ± 22.26	58.54	**0.00**

Table S6. ANOVA test for Circulating gene (PTEN, MMP2 & NF-κβ) and MicroRNA (hsa-miR-181b-5p) expression profiles for T2DM patients, DN patients and healthy control subjects.

Types of Sample	PTEN (Blood)	MMP2 (Blood)	NF-κβ (Blood)	miR-181b-5p (Blood)
Healthy Control (Mean ± SD) (n=36)	1 ± 0.05	1 ± 0.05	1 ± 0.05	1 ± 0.05
T2DM (Mean ± SD) (n=38)	0.84 ± 0.85	0.84 ± 1.03	1.72 ± 1.29	2.09 ± 0.09
DN (Mean ± SD) (n=35)	0.63 ± 0.64	0.70 ± 0.55	1.80 ± 1.29	3.16 ± 2.79
F Value	2.97	1.54	8.74	14.14
P-value	**0.05**	0.22	**0.05**	**0.00**
Trend	Downregulation	Downregulation	Upregulation	Upregulation

Table S7. T-test for Circulating gene (PTEN, MMP2 & NF-κβ) and MicroRNA (hsa-miR-181b-5p) expression profiles for T2DM patients, DN patients and healthy control subjects.

Types of Sample	PTEN (Blood)	MMP2 (Blood)	NF-κβ1 (Blood)	miR-181b-5p (Blood)
T2DM (Mean ± SD) (n=38)	0.84 ± 0.85	0.84 ± 1.03	1.72 ± 1.29	2.09 ± 0.09
DN (Mean ± SD) (n=35)	0.63 ± 0.64	0.70 ± 0.55	1.80 ± 1.29	3.16 ± 2.79
t Value	0.264	0.708	0.309	2.147
P-value	0.064	0.482	0.758	**0.03**
Trend	Downregulation	Downregulation	Upregulation	Upregulation

Table S8. Multinomial logistic regression analysis of circulating gene (PTEN, MMP2 & NF-κβ) and MicroRNA (hsa-miR-181b-5p) expression profiles for T2DM patients, DN patients and healthy control subjects.

	B	Std. Error	Wald	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
						Lower Bound	Upper Bound
PTEN	-0.659	0.457	2.078	0.15	0.517	0.211	1.268
hsa-miR-181b-5p	0.707	0.286	6.136	**0.01**	2.029	1.159	3.551
MMP2	-0.557	0.352	2.499	0.11	0.573	0.287	1.143
NF-kβ	0.872	0.322	7.342	**0.01**	2.392	1.273	4.495

Table S9. T-test for Circulating gene (PTEN, MMP2 & NF-κβ) and MicroRNA (hsa-miR-181b-5p) expression profiles for Insulin Resistance patients and Insulin Sensitive subjects.

Types of Sample	PTEN (Blood)	MMP2 (Blood)	NF-κβ1 (Blood)	miR-181b-5p (Blood)
Insulin Sensitive (n=36)	1 ± 0.05	1 ± 0.05	1 ± 0.05	1 ± 0.05
Insulin Resistance (n=47)	0.70 ± 0.57	0.77 ± 0.69	1.83 ± 1.02	2.698 ± 2.30
t-value	3.268	2.146	5.507	4.947
p-value	**0.002**	0.38	**0.000**	**0.000**
Trend	Downregulation	Downregulation	Upregulation	Upregulation

Table 10. ANOVA test for Circulating gene (PTEN, MMP2 & NF-κβ) and MicroRNA (hsa-miR-181b-5p) expression profiles for T2DM (Insulin Resistance) & DN (Insulin Resistance) patients and healthy control (Insulin Sensitive) subjects.

Types of Sample	PTEN (Blood)	MMP2 (Blood)	NF-κβ1 (Blood)	miR-181b-5p (Blood)
Healthy Control (Insulin Sensitive) (n=36)	1 ± 0.05	1 ± 0.05	1 ± 0.05	1 ± 0.05
T2DM (Insulin Resistance) (n=23)	0.75 ± 0.62	0.83 ± 0.78	1.82 ± 1.67	2.19 ± 0.89
DN (Insulin Resistance) (n=24)	0.66 ± 0.52	0.71 ± 0.58	1.84 ± 0.88	3.14 ± 2.96
Student's t-value	0.495	0.603	0.064	1.494
p-value	0.623	0.553	0.949	0.147
Trend	Downregulation	Downregulation	No change	Upregulation

Table S11. ANOVA test for Circulating gene (PTEN, MMP2 & NF-κβ) and MicroRNA (hsa-miR-181b-5p) expression profiles for five stages of chronic kidney disease.

Stages	Stages of CKD	GFR	% of Kidney Function	MMP2 (FCE) (Mean ± SD)	PTEN (FCE) (Mean ± SD)	NF-κβ (FCE) (Mean ± SD)	hsa-miR-181b-5p (FCE) (Mean ± SD)
Stage:1	Normal kidney function	90 or Higher	90-100	0.904 ± 0.822	0.923 ± 0.662	1.152 ± 0.818	1.412 ± 0.618
Stage:2	Kidney damage with mild loss of kidney function	89-60	89-60	0.900 ± 0.355	0.908 ± 0.319	1.438 ± 0.779	2.194 ± 2.764
Stage:3	3a: kidney damage with mild to moderate

3b: Moderate to severe loss of kidney function | 59-30 | 59-30 | 0.678 ± 0.541 | 0.569 ± 0.482 | 1.629 ± 0.837 | 2.229 ± 0.845 |
Stage:4	Severe loss of kidney function	44-30	44-30	0.621 ± 0.541	0.476 ± 0.572	1.811 ± 0.721	2.559 ± 2.173
Stage:5	Kidney failure	29-15	29-15	0.335 ± 0.179	0.417 ± 0.117	1.908 ± 0.587	3.555 ± 2.161
F-value				1.079	2.431	2.458	2.399
p-Value				0.372	**0.05**	**0.05**	**0.05**
Trend				Downregulation	Downregulation	Upregulation	Upregulation

Table S12. Pathway enrichment (KEGG Pathways) analysis for PPI Genes by STRING database.

KEGG Pathways	Negative log10 (FDR)	False Discovery Rate	matching proteins in your network (labels)
T cell receptor signaling pathway	6.96	0.00	NF-κβIA, NF-κβ1, CHUK, RELA, PIK3R1
Insulin resistance	6.90	0.00	NF-κβIA, NF-κβ1, PTEN, RELA, PIK3R1
PI3K-Akt signaling pathway	6.12	0.00	NF-κβ1, TP53, CHUK, PTEN, RELA, PIK3R1
Th1 and Th2 cell differentiation	5.50	0.00	NF-κβIA, NF-κβ1, CHUK, RELA
IL-17 signaling pathway	5.43	0.00	NF-κβIA, NF-κβ1, CHUK, RELA
AGE-RAGE signaling pathway in diabetic complications	5.33	0.00	MMP2, NF-κβ1, RELA, PIK3R1
Endocrine resistance	3.64	0.00	MMP2, TP53, PIK3R1
mTOR signaling pathway	3.09	0.00	CHUK, PTEN, PIK3R1

Table S13. Gene Ontology (Biological Process) analysis for PPI Genes by STRING database.

Biological Process	false discovery rate	Negative log10 (FDR)	Genes
Response to cytokine	0.00	6.62	NF-κβIA, TIMP1, MMP2, RELB, NF-κβ1, TIMP2, TP53, CHUK, RELA, PIK3R1
I-kappaB kinase/NF-kappaB signaling	0.00	5.53	NF-κβIA, RELB, NF-κβ1, CHUK, RELA
Regulation of phosphatidylinositol 3-kinase signaling	0.00	3.46	SLC9A3R1, PTEN, NEDD4, PIK3R1
T cell receptor signaling pathway	0.00	3.10	NF-κβ1, CHUK, RELA, PIK3R1
Extracellular matrix disassembly	0.00	2.74	TIMP1, MMP2, TIMP2
Inflammatory response	0.00	2.70	TIMP1, RELB, NF-κβ1, CHUK, RELA
Phosphatidylinositol 3-kinase signaling	0.02	1.74	PTEN, PIK3R1
Response to insulin	0.03	1.58	PTEN, RELA, PIK3R1

Table S14. Gene Ontology (Molecular Functions) analysis for PPI Genes by STRING database.

Molecular Functions	false discovery rate	Negative Log10 (FDR)	Gene Symbols
Enzyme binding	0.00	4.83	NF-κβIA, TIMP1, RELB, NF-κβ1, SLC9A3R1, TIMP2, TP53, PTEN, RELA, NEDD4, PIK3R1
Signaling receptor binding	0.00	2.37	TIMP1, SLC9A3R1, TIMP2, TP53, CHUK, PTEN, NEDD4, PIK3R1
Protein-containing complex binding	0.01	2.27	SLC9A3R1, TIMP2, TP53, CHUK, PTEN, RELA, PIK3R1
beta-2 adrenergic receptor binding	0.01	2.19	SLC9A3R1, NEDD4
Protein binding	0.02	1.66	NF-κβIA, TIMP1, RELB, NF-κβ1, SLC9A3R1, TIMP2, TP53, CHUK, PTEN, RELA, NEDD4, PIK3R1
Transcription factor binding	0.02	1.66	NF-κβIA, NF-κβ1, TP53, RELA, PIK3R1
Metalloendopeptidase inhibitor activity	0.02	1.66	TIMP1, TIMP2
Molecular function regulator	0.02	1.66	TIMP1, RELB, NF-κβ1, SLC9A3R1, TIMP2, TP53, RELA, NEDD4, PIK3R1
Protein tyrosine kinase binding	0.02	1.66	TP53, PTEN, PIK3R1

Table S15. The Validation of fold change expression for PPI interacting and key genes in three different microarray datasets of circulating T2DM and healthy subjects.

Gene Symbols	Healthy Control		T2DM (GSE156993)		T2DM (GSE9006)		T2DM (GSE21321)		
	Fold Expression	Change	Fold Change Expression	P Value	Fold Change Expression	P Value	Fold Expression	Change	P Value
CHUK	1.00		1.04	0.58	1.18	0.18	0.98		0.90
MMP2	1.00		0.94	0.21	0.62	0.01	0.74		0.41
NEDD4	1.00		1.07	0.53	1.32	0.00	0.87		0.54
NF-κβ1	1.00		1.17	0.27	1.32	0.00	1.05		0.76
NF-κβIA	1.00		0.91	0.26	0.79	0.16			
PTEN	1.00		0.78	0.02	0.84	0.02	0.9		0.64
RELA	1.00		1	0.57	1.01	0.10			
RELB	1.00		1	0.42	0.86	0.20	1.54		0.15
SLC9A3R1	1.00		0.87	0.20	0.94	0.54	1		0.72
TIMP1	1.00		1.02	0.14	1.2	0.08	1.02		0.95
TIMP2	1.00		0.98	0.20	0.88	0.31	0.94		0.65
TP53	1.00		0.94	0.50	0.75	0.00	1		0.99

Table S16. The Validation of fold change expression for hsa-miR-181b-5p in three different microarray datasets (GSE21321) of circulating T2DM and healthy subjects.

ID	P.Value	t	B	Fold Change	logFC	Gene.symbol	Gene.title
1852	0.028861	1.094422	-6.38	1.343228	0.425704	hsa-miR-181b	AACAUUCAUUGCUGUCGGUGGGU

Table S17. The Validation of fold change expression for hsa-miR-181b-5p in three different microarray datasets (GSE51674) of kidney tissue of T2DM and healthy subjects.

ID	P.Value	t	B	Fold Change	logFC	ORGANISM	miRNA_ID
hsa-miR-181b	0.03	2.57	-4.58	3.31	9.93296893853	Homo sapiens	hsa-miR-181b