SUPPLEMENTARY DATA

KIDNEY INJURY MOLECULE – 1 (KIM-1) AND THE LOSS OF KIDNEY FUNCTION IN DIABETIC NEPHROPATHY: A LIKELY CAUSAL LINK IN PATIENTS WITH TYPE 1 DIABETES

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Contents

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SUPPLEMENTARY DATA

Supplementary Table 1. Baseline data of patients with type 1 diabetes included in the study regarding progression at all stages of DN.

Data are presented as means ± standard deviations (SD), median (interquartile range) or percentages (%).

Variable		Normal AER		P	Microalbuminuria		P	Macroalbuminuria		P
		Non-progressors	Progressors to microalbuminuria		Non-progressors	Progressors to macroalbuminuria		Non-progressors	Progressors to ESRD	
Number of patients (M/F)		900 (377/523)	53 (30/23)	< 0.05	225 (130/95)	44 (33/11)	< 0.05	274 (146/128)	77 (45/32)	0.50
Age (years)		40.2 ± 12.0	38.8 ± 13.4	0.43	39.5 ± 13.0	37.8 ± 11.3	0.43	42.0 ± 10.6	41.1 ± 10.3	0.51
Age of onset (years)		15.8 ± 9.0	16.8 ± 10.0	0.44	13.1 ± 9.1	11.4 ± 9.2	0.26	12.5 ± 8.6	13.0 ± 8.4	0.66
Duration (years)		24.4 ± 10.0	22.0 ± 10.5	0.09	26.4 ± 10.8	26.4 ± 10.2	0.99	29.4 ± 8.1	28.0 ± 7.7	0.18
BMI (kg/m^2)		25.1 ± 3.4	26.1 ± 3.7	0.04	25.6 ± 3.5	25.4 ± 3.6	0.72	25.8 ± 3.5	26.0 ± 4.9	0.89
WHR	Men	0.90 ± 0.07	0.94 ± 0.06	0.001	0.91 ± 0.07	0.94 ± 0.06	0.05	0.94 ± 0.07	0.95 ± 0.08	0.18
	Women	0.80 ± 0.06	0.81 ± 0.09	0.32	0.82 ± 0.06	0.88 ± 0.09	0.005	0.84 ± 0.07	0.84 ± 0.06	0.89
History of smoking (%)		39.5	55.8	0.02	50.9	68.1	0.05	59.6	66.2	0.36
SBP (mmHg)		131 ± 16	132 ± 16	0.82	137 ± 18	138 ± 17	0.60	142 ± 19	150 ± 22	0.003
DBP (mmHg)		78 ± 9	79 ± 12	0.75	81 ± 10	83 ± 10	0.36	81 ± 9	85 ± 10	0.02
HbA_{1C} (mmol/mol)		65 ± 5	76 ± 7	< 0.001	70 ± 7	83 ± 8	< 0.001	75 ± 7	78 ± 10	0.08
HbA_{1C} (%)		8.1 ± 1.2	9.1 ± 1.4	< 0.001	8.6 ± 1.4	9.7 ± 1.8	< 0.001	9.0 ± 1.4	9.3 ± 2.0	0.08
Total cholesterol (mmol/l)		4.87 ± 0.86	5.27 ± 0.89	0.09	5.00 ± 0.88	4.93 ± 0.87	0.03	5.29 ± 0.88	5.85 ± 1.62	< 0.001
HDL cholesterol (mmol/l)		1.37 ± 0.37	1.28 ± 0.38	0.09	1.31 ± 0.37	1.19 ± 0.39	0.09	1.23 ± 0.34	1.15 ± 0.45	0.10
LDL cholesterol (mmol/l)		3.02 ± 0.79	3.17 ± 0.78	0.22	3.08 ± 0.76	3.30 ± 0.88	< 0.05	3.38 ± 0.83	3.50 ± 1.10	0.32
Triglycerides (mmol/l)		0.90 (0.70 – 1.23)	1.16 (0.89 – 1.61)	< 0.001	1.05 (0.80 – 1.44)	1.49 (0.95 – 2.20)	< 0.001	1.53 (0.96 – 1.85)	1.80 (1.17 – 2.80)	< 0.001
AER (mg/24h)		7 (5 – 11)	13.05 (8 – 23)	< 0.001	45 (25 – 87)	151 (89 – 220)	< 0.001	335 (144 – 832)	1530 (689 – 2997)	< 0.001
eGFR (ml/min/1.73 m^2)		88 ± 28	85 ± 28	0.46	87 ± 37	92 ± 49	0.46	57 ± 27	23 ± 22	< 0.001
KIM-1 (ɳ g/mmol)		27.7 (13.4 – 50.3)	30.0 (16.7 – 48.3)	0.62	31.7 (15.9 – 62.4)	43.8 (22.5 – 74.6)	0.04	43.2 (21.2 – 73.6)	100.5 (52.1 - 172.7)	< 0.0001

BMI – body mass index, WHR – waist to hip ratio, SBP – systolic blood pressure, DBP – diastolic blood pressure, HbA_{1C} – glycated hemoglobin A1c, HDL cholesterol – high density lipoprotein cholesterol, LDL cholesterol – low density lipoprotein cholesterol, AER – urinary albumin excretion rate, eGFR – estimated glomerular filtration rate, KIM-1 – ratio of urinary kidney injury molecule – 1 and urinary creatinine, ESRD – end stage renal disease.

SUPPLEMENTARY DATA

Supplementary Table 2. Basic models for progression using Cox regression analysis with baseline data. Basic models of progression build from the baseline clinical and laboratory values significantly associated with progression of DN, using Cox proportional hazard models with backward selection of covariates.

Progression to microalbuminuria				Progression to macroalbuminuria				Progression to ESRD			
Variable	Multivariable Cox proportional hazard model (backward selection)			Variable	Multivariable Cox proportional hazard model (backward selection)			Variable	Multivariable Cox proportional hazard model (backward selection)		
	HR	95% CI	P		HR	95% CI	P		HR	95% CI	P
HbA1c (%)	1.50	1.23 – 1.83	0.0001	HbA1c (%)	1.23	1.08 – 1.41	<0.01	ln(triglycerides)	2.7	1.81 – 4.01	<0.0001
ln(triglycerides)	1.79	1.10 – 2.91	0.02	ln(triglycerides)	2.14	1.20 – 3.84	0.01	SBP (mmHg)	1.02	1.01 – 1.03	<0.001
WHR	61.47	2.71 – 1393.26	0.01	WHR	356.17	5.93 - 21383.11	<0.01				

HbA_{1C} – glycated hemoglobin A1c, ln(triglycerides) – natural logarithm from triglycerides, WHR – waist to hip ratio, SBP – systolic blood pressure, ESRD – end stage renal disease, HR – hazard ratio.

Supplementary Table 3. ROC curves analysis for the main comparisons between KIM-1, AER and eGFR.

Receiver operating characteristic (ROC)	AUC	SE	95%CI	Differences between AUCs									
				KIM-1		AER		eGFR		KIM-1 & AER		KIM-1 & eGFR	
				Difference	p	Difference	p	Difference	p	Difference	p	Difference	p
KIM-1	0.735	0.033	0.686 – 0.781	-	-	0.062	0.07	0.126	0.003	0.062	0.08	0.130	0.001
AER	0.797	0.01	0.751 – 0.838	0.062	0.07	-	-	0.065	0.10	0.000	1.00	0.06	0.08
KIM-1 & AER	0.797	0.031	0.751 – 0.838	0.062	0.08	0.000	1.00	0.065	0.11	-	-	0.06	0.08
eGFR	0.861	0.029	0.821 – 0.896	0.126	0.003	0.065	0.10	-	-	0.065	0.11	0.004	0.56
KIM-1 & eGFR	0.865	0.028	0.825 – 0.899	0.130	0.001	0.06	0.08	0.004	0.57	0.06	0.09	-	-

KIM-1 – univariate analysis for KIM-1; AER – univariate analysis for AER; KIM-1 & AER – Cox regression model with KIM-1 plus AER in the model without any correction; eGFR– univariate analysis for eGFR; KIM-1 & eGFR – Cox regression model with KIM-1 plus eGFR in the model without any supplementary adjustments; AER – urinary albumin excretion rate, KIM-1 – kidney injury molecule – 1, eGFR – estimated glomerular filtration rate. Delong et al. (1988) method was used for the calculation of the standard error (SE) of the Area Under the Curve (AUC), confidence intervals (95% CI) and of the difference between two AUCs.

SUPPLEMENTARY DATA

Supplementary Table 4. Reclassification improvement indexes calculations. The discrimination improvement given by the addition of urinary KIM-1 to either AER alone, basic progression models plus AER (AER&PM) or basic progression model plus AER and eGFR (AER&eGFR&PM) assessed by calculating category-less net reclassification improvement (continuous NRI), integrated discrimination improvement (IDI).

	Continuous NRI	95% CI	IDI	95% CI
Progression to ESRD				
KIM-1&AER vs AER	0.264	-0.161 – 0.578	0.024	-0.000 – 0.073
KIM-1&AER&PM vs AER&PM	0.243	-0.070 – 0.592	0.023	-0.000 – 0.073
KIM-1&AER&eGFR&PM vs AER&eGFR&PM	0.327	-0.079 – 0.663	0.020	-0.003 – 0.058

ESRD – end stage renal disease; KIM-1 – kidney injury molecule 1; AER – albumin excretion rate; eGFR – estimated glomerular filtration rate; PM – basic model for progression to ESRD (Supplemental Table 1); AER&PM – model formed by addition of AER to the basic model for progression to ESRD; KIM-1&AER&PM – model formed by addition of KIM-1 to AER&PM; AER&eGFR&PM – model formed by addition of AER and eGFR to the basic model for progression to ESRD; KIM-1&AER&eGFR&PM – model formed by addition of KIM-1 to AER&eGFR&PM.

SUPPLEMENTARY DATA

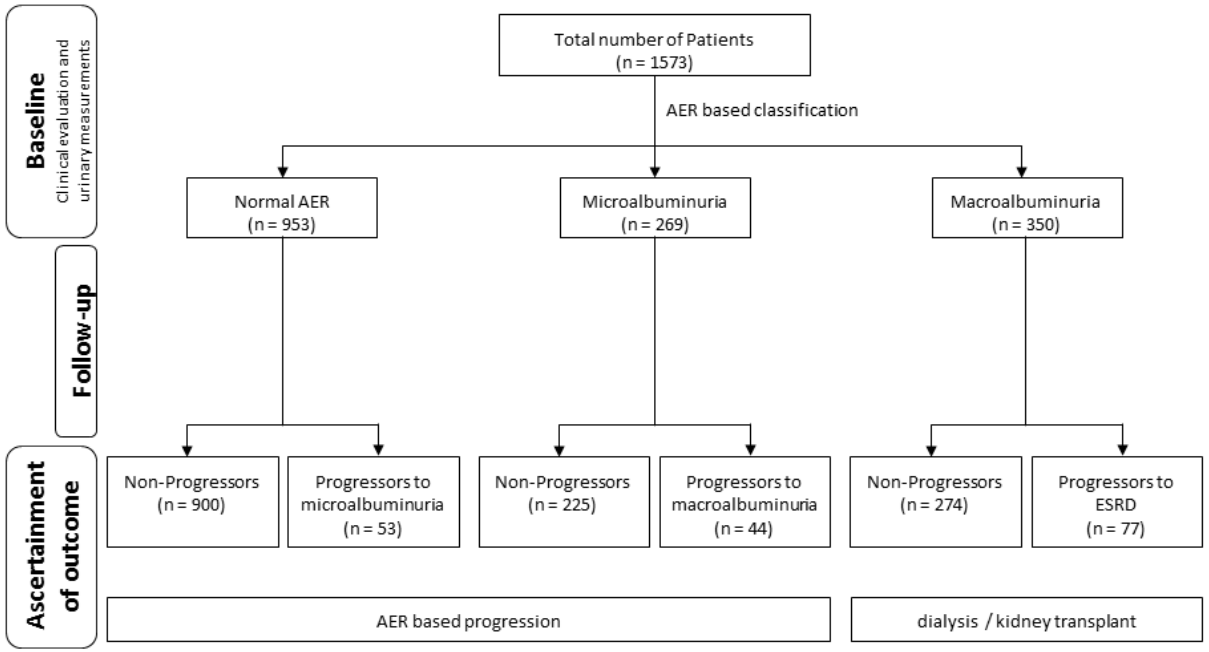
Supplementary Table 5. Top SNPs associated with KIM-1 levels. Models were adjusted for diabetes duration and two first principal components (PCs).

CHR	SNP	BP	A1	A2	MAF	β	95% CI	*P*	*P adjusted for* rs2036402
5	rs2036402	156396820	C	T	0.24	-0.51	-0.47 – -0.54	6.48×10^{-38}	NA
5	rs6889164	156399356	C	T	0.24	-0.51	-0.47 – -0.54	6.83×10^{-38}	NA
5	rs13173581	156402386	T	C	0.24	-0.5	-0.47 – -0.54	7.71×10^{-38}	NA
5	rs1039438	156409348	A	G	0.24	-0.5	-0.47 – -0.54	7.81×10^{-38}	NA
5	rs12522248	156412004	C	T	0.26	-0.49	-0.46 – -0.53	4.45×10^{-37}	0.18
5	rs11740496	156367980	G	A	0.24	-0.5	-0.46 – -0.54	1.29×10^{-36}	0.73
5	rs11740499	156364319	A	G	0.24	-0.5	-0.46 – -0.54	1.54×10^{-36}	0.71
5	rs12515585	156362728	G	A	0.24	-0.5	-0.46 – -0.54	1.76×10^{-36}	0.68
5	rs7719994	156362654	C	T	0.24	-0.5	-0.46 – -0.54	1.79×10^{-36}	0.68
5	rs13169621	156359552	A	G	0.23	-0.51	-0.48 – -0.56	2.46×10^{-36}	0.93
5	rs13181803	156361755	G	C	0.24	-0.5	-0.46 – -0.54	4.05×10^{-36}	0.50
5	rs13169465	156359494	A	G	0.24	-0.5	-0.46 – -0.54	4.40×10^{-36}	0.49
5	rs13169155	156359241	A	G	0.24	-0.5	-0.46 – -0.54	4.55×10^{-36}	0.48
5	rs6863148	156339221	A	G	0.24	-0.5	-0.46 – -0.54	8.76×10^{-36}	0.43
5	rs7700944	156298759	A	G	0.21	-0.51	-0.47 – -0.55	5.11×10^{-32}	0.89
5	rs6555760	156297944	A	T	0.21	-0.51	-0.47 – -0.55	6.36×10^{-32}	0.89
5	rs2862058	156287953	G	A	0.21	-0.51	-0.47 – -0.55	7.24×10^{-32}	0.89
5	rs1345617	156284081	C	G	0.21	-0.51	-0.47 – -0.55	8.47×10^{-32}	0.89
5	rs1345618	156283925	C	T	0.21	-0.5	-0.46 – -0.55	8.97×10^{-32}	0.89
5	rs2279804	156411782	T	C	0.42	-0.4	-0.37 – -0.43	3.04×10^{-29}	0.0001
5	rs953568	156410210	A	T	0.42	-0.4	-0.37 – -0.43	3.61×10^{-29}	0.0001
5	rs953569	156409978	G	T	0.41	-0.4	-0.37 – -0.43	4.39×10^{-29}	0.0006
5	rs6555820	156404727	A	C	0.41	-0.4	-0.37 – -0.42	5.47×10^{-29}	0.0007
5	rs868529	156363714	T	A	0.40	-0.39	-0.36 – -0.42	8.52×10^{-28}	0.002
5	rs1393206	156362231	A	T	0.20	-0.47	-0.43 – -0.51	6.05×10^{-26}	0.08
5	rs7732745	156279792	T	C	0.18	-0.42	-0.38 – -0.46	6.72×10^{-21}	0.12
5	rs10070224	156278313	C	T	0.16	-0.47	-0.42 – -0.52	7.45×10^{-21}	0.69
5	rs12187482	156269565	G	A	0.16	-0.47	-0.42 – -0.52	7.48×10^{-21}	0.69
5	rs7720464	156268109	G	A	0.15	-0.49	-0.44 – -0.54	2.05×10^{-20}	0.62
5	rs4704821	156267542	A	C	0.15	-0.49	-0.44 – -0.55	8.16×10^{-20}	0.58
5	rs2116787	156432559	G	A	0.15	-0.43	-0.39 – -0.47	1.97×10^{-18}	0.86
5	rs12516270	156420050	A	G	0.18	-0.41	-0.37 – -0.44	4.16×10^{-18}	0.27
5	rs4704828	156338586	A	T	0.39	-0.31	-0.29 – -0.33	8.57×10^{-18}	0.71
5	rs6873137	156366831	T	C	0.39	-0.3	-0.28 – -0.33	1.71×10^{-17}	0.52
5	rs10076475	156354809	G	A	0.39	-0.3	-0.28 – -0.33	1.90×10^{-17}	0.53
5	rs13360569	156355465	T	C	0.39	-0.3	-0.28 – -0.33	1.92×10^{-17}	0.53
5	rs9790967	156367233	G	T	0.39	-0.31	-0.28 – -0.33	2.19×10^{-17}	0.50
5	rs1501909	156398757	T	G	0.45	0.3	0.28 – 0.32	6.39×10^{-17}	0.02
5	rs17054137	156405508	A	G	0.45	0.3	0.28 – 0.32	6.52×10^{-17}	0.02
5	rs1546288	156363283	A	G	0.45	0.29	0.27 – 0.31	2.42×10^{-16}	0.03
5	rs2277025	156392673	C	T	0.45	0.29	0.27 – 0.31	3.30×10^{-16}	0.04
5	rs4704728	156339186	C	G	0.45	0.29	0.27 – 0.31	4.41×10^{-16}	0.03
5	rs17649946	156268084	T	C	0.06	-0.7	-0.59 – -0.84	5.72×10^{-15}	0.17
5	rs17054136	156405403	A	G	0.05	-0.63	-0.53 – -0.75	1.06×10^{-11}	0.11
5	rs4704820	156267259	G	T	0.10	-0.42	-0.37 – -0.48	9.68×10^{-11}	0.12
5	rs13171055	156192173	T	A	0.07	-0.48	-0.42 – -0.56	1.04×10^{-10}	0.90
5	rs13190208	156250375	T	C	0.07	-0.46	-0.4 – -0.53	4.90×10^{-10}	0.89
5	rs17054104	156352343	T	C	0.20	0.27	0.25 – 0.3	1.04×10^{-9}	0.004
5	rs2434708	156163554	A	C	0.40	-0.2	-0.19 – -0.22	2.38×10^{-8}	0.16

KIM-1 – kidney injury molecule – 1. Since KIM-1 had a non-normal distribution its values have been logarithmic transformed to ln(KIM-1), after normalization for urinary creatinine; CHR – chromosome; BP – base pair position; A1 – minor allele. A2 – major allele; MAF – minor allele frequency; B – effect on ln(KIM-1) per one copy of A1; P – statistical significance of the association between SNPs and ln(KIM-1) acording to models adjusted for diabetes duration and two first PCs; P adjusted for rs2036402 – statistical significance of the association between SNPs and ln(KIM-1) after addition to the previous model of rs2036402, as an independent covariate. P values considered statistical significant were less than 10^{-8}.

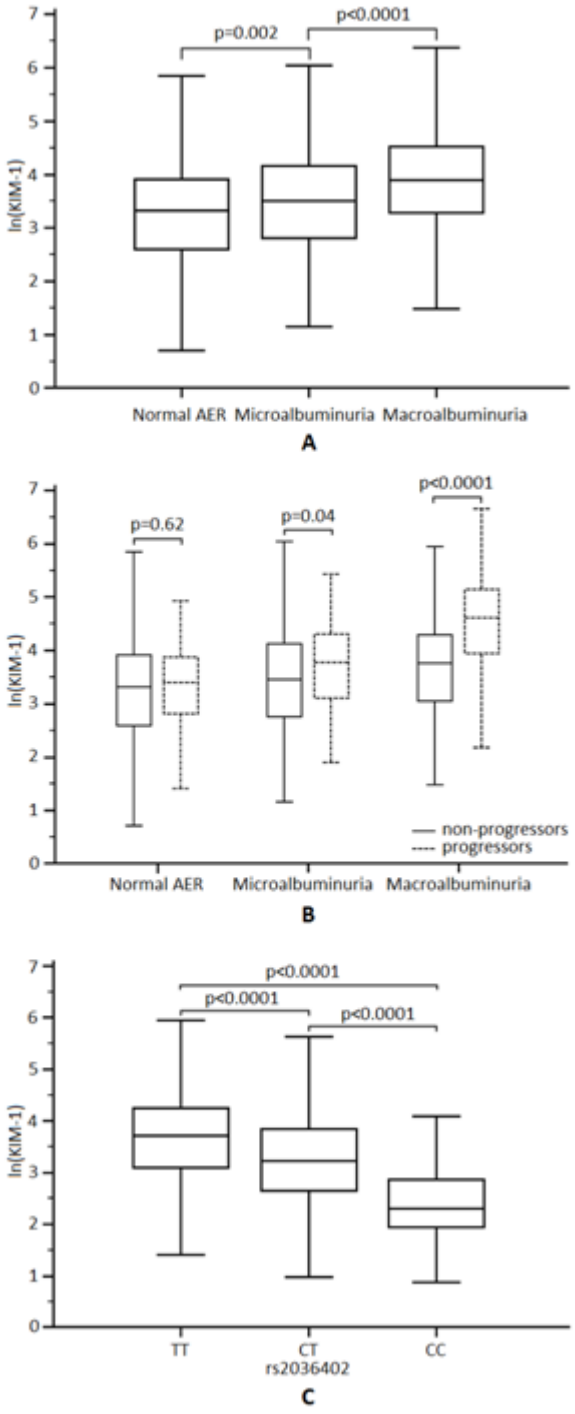
SUPPLEMENTARY DATA

Supplementary Figure 1. Study Flow Diagram. At baseline we had 1573 patients with data for all variable of interest.
According to baseline data patients were divided into three groups according to AER categories, into those with normal AER (<30 mg/24 h or <20 µg/min), microalbuminuria (30–300 mg/24 h or 20-200 µg/min) and macroalbuminuria (>300 mg/24 h or >200 µg/min). At baseline we had three groups: 953 patients had normal AER, 269 patients had microalbuminuria and 350 had macroalbuminuria. After a median follow-up of 6.0 years, 53 patients progressed from normal AER to microalbuminuria, 44 patients progressed from microlabuminuria to macroalbuminuria and 77 patients progressed from macroalbuminuria to end stage renal disease (ESRD). Progression of DN was defined based on AER thresholds described above, as the passage from one of the categories to the next stage. Progression to ESRD was defined as de novo requirement of dialysis or kidney transplantation.



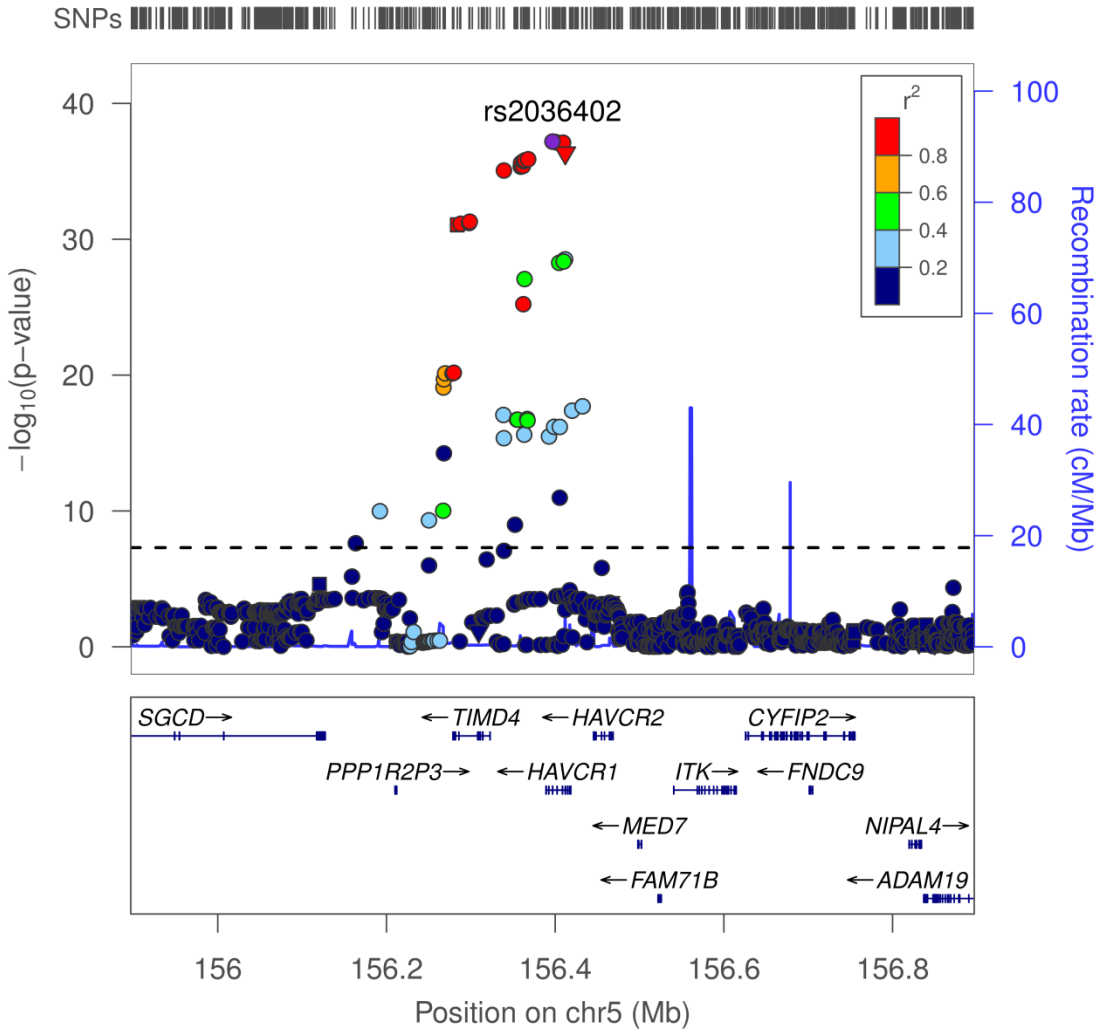
SUPPLEMENTARY DATA

Supplementary Figure 2. Distribution of urinary KIM-1 levels. A: Urinary KIM-1 levels across study groups at the baseline in relation with initial AER based stage. The KIM-1 levels were significantly different between all study groups (p<0.001). **B:** Urinary KIM-1 levels across DN groups at the baseline in relation with progression status. KIM-1 levels were significantly higher for progressors in the microalbuminuria group (p=0.04) and macroalbuminuria group (p<0.0001), when compared with non-progressors. **C:** Urinary KIM-1 levels according to genotypes. KIM-1 levels were significantly different regarding the genotypes (p<0.0001).



SUPPLEMENTARY DATA

Supplementary Figure 3. Regional association plot of the SNPs associated with urinary KIM1 levels. The dashed horizontal line indicates the genome-wide significant $P<5\times10^{-8}$. The association analysis was adjusted for sex, diabetes duration, and the two first principal components (PCs). The plot was made with the LocusZoom software[1] ([http://csg.sph.umich.edu/locuszoom/).



SUPPLEMENTARY DATA

[1] Pruim RJ*, Welch RP*, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, Abecasis GR, Willer CJ. (2010) LocusZoom: Regional visualization of genome-wide association scan results. *Bioinformatics* 26(18): 2336.2337, 2010

Online-only Appendix - The complete list of physicians and nurses at each center participating in the collection of patients**:**

Anjalankoski Health Center: S. Koivula and T. Uggeldahl; Central Finland Central Hospital: T. Forslund, A. Halonen, A. Koistinen, P. Koskiaho, M. Laukkanen, J. Saltevo and M. Tiihonen; Central Hospital of Åland Islands: M. Forsen, H. Granlund, A.-C. Jonsson and B. Nyroos; Central Hospital of Kanta-Häme: P. Kinnunen, A. Orvola, T. Salonen and A. Vähänen; Central Hospital of Kymenlaakso: R. Paldanius, M. Riihelä and L. Ryysy; Central Hospital of Länsi-Pohja: H. Laukkanen, P. Nyländen and A. Sademies; Central Ostrobothnian Hospital District: S. Anderson, B. Asplund, U. Byskata, P. Liedes, M. Kuusela and T. Virkkala; City of Espoo Health Center (Espoonlahti): A. Nikkola and E. Ritola; (Tapiola): M. Niska and H. Saarinen; (Viherlaakso): A. Lyytinen; City of Helsinki Health Center (Puistola): H. Kari and T. Simonen; (Suutarila): A. Kaprio, J. Kärkkäinen and B. Rantaeskola; (Töölö): P. Kääriäinen, J. Haaga and A-L. Pietiläinen; City of Hyvinkää Health Center: S. Klemetti, T. Nyandoto, E. Rontu and S. Satuli-Autere; City of Vantaa Health Center (Korso): R. Toivonen and H. Virtanen; (Länsimäki): R. Ahonen, M. Ivaska-Suomela and A. Jauhiainen; (Martinlaakso): M. Laine, T. Pellonpää and R. Puranen; (Myyrmäki): A. Airas, J. Laakso and K. Rautavaara; (Rekola): M. Erola and E. Jatkola; (Tikkurila): R. Lönnblad, A. Malm, J. Mäkelä and E. Rautamo; Heinola Health Center: P. Hentunen and J. Lagerstam; Helsinki University Central Hospital (Department of Medicine, Division of Nephrology): D. Gordin, J. Fagerudd, M. Feodoroff, O. Heikkilä, L. Kyllönen, J. Kytö, K. Pettersson-Fernholm, M. Rosengård-Bärlund, M. Rönnback, and J. Wadén; Herttoniemi Hospital: V. Sipilä; Hospital of Lounais-Häme: T. Kalliomäki, J. Koskelainen, R. Nikkanen, N. Savolainen, H. Sulonen and E. Valtonen; Iisalmi Hospital: E. Toivanen; Jokilaakso Hospital: A. Parta and I. Pirttiniemi; Jorvi Hospital: S. Aranko, S. Ervasti, R. Kauppinen-Mäkelin, A. Kuusisto, T. Leppälä, K. Nikkilä and L. Pekkonen; Jyväskylä Health Center: K. Nuorva and M. Tiihonen; Kainuu Central Hospital: S. Jokelainen, P. Kemppainen, A-M. Mankinen and M. Sankari; Kerava Health Center: H. Stuckey and P. Suominen; Kirkkonummi Health Center: A. Lappalainen, M. Liimatainen and J. Santaholma; Kivelä Hospital: A. Aimolahti and E. Huovinen; Koskela Hospital: V. Ilkka and M. Lehtimäki; Kotka Health Center: E. Pälikkö-Kontinen and A. Vanhanen; Kouvola Health Center: E. Koskinen and T. Siitonen; Kuopio University Hospital: E. Huttunen, R. Ikäheimo, P. Karhapää, P. Kekäläinen, M. Laakso, T. Lakka, E. Lampainen, L. Moilanen, L. Niskanen, U. Tuovinen, I. Vauhkonen and E. Voutilainen; Kuusamo Health Center: T. Kääriäinen and E. Isopoussu; Kuusankoski Hospital: E. Kilkki, I. Koskinen and L. Riihelä; Laakso Hospital, Helsinki: T. Meriläinen, P. Poukka, R. Savolainen and N. Uhlenius; Lahti City Hospital: A. Mäkelä and M. Tanner; Lapland Central Hospital: L. Hyvärinen, S. Severinkangas and T. Tulokas; Lappeenranta Health Center: P. Linkola and I. Pulli; Lohja Hospital: T. Granlund, M. Saari and T. Salonen; Länsi-Uusimaa Hospital: I.-M. Jousmaa and J. Rinne; Loimaa Health Center: A. Mäkelä and P. Eloranta; Malmi Hospital: H. Lanki, S. Moilanen and M. Tilly-Kiesi; Mikkeli Central Hospital: A. Gynther, R. Manninen, P. Nironen, M. Salminen and T. Vänttinen; Mänttä Regional Hospital: I. Pirttiniemi and A-M. Hänninen; North Karelian Hospital: U-M. Henttula, P. Kekäläinen, M. Pietarinen, A. Rissanen and M. Voutilainen; Nurmijärvi Health Center: A. Burgos and K. Urtamo; Oulaskangas Hospital: E. Jokelainen, P.-L. Jylkkä, E. Kaarlela and J. Vuolaspuro; Oulu Health Center: L. Hiltunen, R. Häkkinen and S. Keinänen-Kiukaanniemi; Oulu University Hospital: R. Ikäheimo; Päijät-Häme Central Hospital: H. Haapamäki, A. Helanterä, S. Hämäläinen, V. Ilvesmäki and H. Miettinen; Palokka Health Center: P. Sopanen and L. Welling; Pieksämäki Hospital: V. Javtsenko and M. Tamminen; Pietarsaari Hospital: M-L. Holmbäck, B. Isomaa and L. Sarelin; Pori City Hospital: P. Ahonen, P. Merensalo and K. Sävelä;

SUPPLEMENTARY DATA

Porvoo Hospital: M. Kallio, B. Rask and S. Rämö; Raahe Hospital: A. Holma, M. Honkala, A. Tuomivaara and R. Vainionpää; Rauma Hospital: K. Laine, K. Saarinen and T. Salminen; Riihimäki Hospital: P. Aalto, E. Immonen and L. Juurinen; Salo Hospital: A. Alanko, J. Lapinleimu, P. Rautio and M. Virtanen; Satakunta Central Hospital: M. Asola, M. Juhola, P. Kunelius, M.-L. Lahdenmäki, P. Pääkkönen and M. Rautavirta; Savonlinna Central Hospital: T. Pulli, P. Sallinen, M. Taskinen, E. Tolvanen, H. Valtonen and A. Vartia; Seinäjoki Central Hospital: E. Korpi-Hyövälti, T. Latvala and E. Leijala; South Karelia Central Hospital: T. Ensala, E. Hussi, R. Härkönen, U. Nyholm and J. Toivanen; Tampere Health Center: A. Vaden, P. Alarotu, E. Kujansuu, H. Kirkkopelto-Jokinen, M. Helin, S. Gummerus, L. Calonius, T. Niskanen, T. Kaitala and T. Vatanen; Tampere University Hospital: I. Ala-Houhala, T. Kuningas, P. Lampinen, M. Määttä, H. Oksala, T. Oksanen, K. Salonen, H. Tauriainen and S. Tulokas; Tiirismaa Health Center: T. Kivelä, L. Petlin and L. Savolainen; Turku Health Center: I. Hämäläinen, H. Virtamo and M. Vähätalo; Turku University Central Hospital: K. Breitholz, R. Eskola, K. Metsärinne, U. Pietilä, P. Saarinen, R. Tuominen and S. Äyräpää; Vaajakoski Health Center: K. Mäkinen and P. Sopanen; Valkeakoski Regional Hospital: S. Ojanen, E. Valtonen, H. Ylönen, M. Rautiainen and T. Immonen; Vammala Regional Hospital: I. Isomäki, R. Kroneld and M. Tapiolinna-Mäkelä; Vaasa Central Hospital: S. Bergkulla, U. Hautamäki, V.-A. Myllyniemi and I. Rusk.