Supplemental Material

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Supplemental Table 1. All Single Nucleotide Polymorphisms (SNPs) spanning KL gene region (+/- 20 Kb). 32 SNPs covering the entire gene with extension to the 5' and 3' flanking regions. 17 SNPs (in normal style) are in high linkage disequilibrium (r2>0.80) with the 15 tag SNPs (in bold style).

	SNP rs code	Chr 13 position (bp)	Alleles	Minor allele	MAF
1	**rs446647**	33571078	T/C	C	0.22
2	**rs367243**	33578412	G/A	A	0.20
3	rs499091	33594156	T/C	C	0.40
4	rs211243	33597933	A/G	G	0.38
5	**rs526906**	33598987	C/T	T	0.14
6	rs525014	33599198	C/T	T	0.29
7	rs541053	33606679	G/A	A	0.46
8	**rs480830**	33606723	T/C	C	0.46
9	rs9536234	33607814	C/T	T	0.15
10	**rs9526984**	33609937	A/G	G	0.09
11	rs7982726	33610711	T/C	C	0.15
12	rs569546	33611114	T/C	C	0.13
13	rs8001148	33611365	A/G	G	0.15
14	rs9526998	33613579	G/A	A	0.15
15	**rs1334928**	33615948	T/G	G	0.38
16	**rs2320762**	33617174	T/G	G	0.41
17	rs9536282	33617662	C/T	T	0.15
18	**rs657049**	33622817	A/G	G	0.28
19	rs687045	33624889	A/C	C	0.40
20	rs9536314	33628138	T/G	G	0.15
21	**rs9527026**	33628239	G/A	A	0.15
22	rs522796	33630055	T/C	C	0.44
23	**rs9315202**	33642016	C/T	T	0.30
24	rs677332	33643904	A/G	G	0.40
25	**rs581971**	33644398	G/A	A	0.47
26	rs582524	33644537	A/G	G	0.46
27	rs598413	33645766	T/G	G	0.45
28	**rs670657**	33649054	G/A	A	0.17
29	**rs9536357**	33651505	G/A	A	0.46
30	rs9563133	33651873	T/C	C	0.32
31	**rs9591501**	33658270	C/T	T	0.09
32	**rs566996**	33660785	G/A	A	0.25

SNPs are ranked by chromosome and position based on GRCh37 (release 105) assembly.

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Supplemental Table 2. Correlation between alpha-klotho and Creatinine clearance or eGFR at baseline. Data are presented as unadjusted or adjusted for age, sex, BMI.

	Unadjusted		Adjusted	
	R	***P value***	***R***	***P value***
Creatinine clearance (mL/min)	0.16	0.02	0.22	<0.001
eGFR (mL/min/1.73m^2)	0.22	0.001	0.16	0.006

Supplemental Table 3. Correlation between alpha-klotho and changes of systolic BP or diastolic BP at the end of salt infusion. Data are presented as unadjusted or adjusted for age, sex, BMI.

	Unadjusted		Adjusted	
	R	***p value***	***R***	***p value***
Systolic BP change (mmHg)	-0.11	0.08	-0.14	0.04
Diastolic BP change (mmHg)	-0.14	0.03	-0.14	0.04

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Supplemental Table 4. Salt-sensitive and salt-resistant patients' distribution in the discovery naïve hypertensive cohort based on KL rs9536314, rs657049 and rs9527026 genotypes.

			Salt-Resistant	Salt-Sensitive	N
KL_rs9536314	GG	N	6	10	16
		%	37.5%	62.5%	100.0%
	GT	N	92	71	163
		%	56.4%	43.6%	100.0%
	TT	N	338	156	494
		%	68.4%	31.6%	100.0%
	Total	N	436	237	673
X^2 =13.06, p=0.001		%	64.8%	35.2%	100.0%
KL_rs657049	AA	N	180	91	271
		%	66.4%	33.6%	100.0%
	AG	N	141	68	209
		%	67.5%	32.5%	100.0%
	GG	N	20	25	45
		%	44.4%	55.6%	100.0%
	Total	N	341	184	525
X^2 =9.15, p=0.01		%	65.0%	35.0%	100.0%
KL_rs9527026	AA	N	5	9	14
		%	35.7%	64.3%	100.0%
	AG	N	74	56	130
		%	56.9%	43.1%	100.0%
	GG	N	262	119	381
		%	68.8%	31.2%	100.0%
	Total	N	341	184	525
X^2 =11.38, p=0.003		%	65.0%	35.0%	100.0%

KL rs9536314 refers to full discovery cohort (n=673), while rs657049 and rs9527026 refer to GWAS cohort (n=525).

Supplemental Table 5. Baseline clinical characteristics of the discovery naïve hypertensive cohort that underwent the acute saline load according to KL rs9536314 genotypes.

	Parameters	Whole NHP cohort (n=673)	TT (n=494)	TG+GG (n=179)	p ANOVA
Anthropometric	Age (years)	45 ± 10	45 ± 10	45± 10	0.87
	Sex (F/M) [a]	126 (18.7)/547 (81.3)	95 (19.2)/399 (80.8)	31 (24.6)/148 (83.4)	0.57
	BMI (kg/m^2)	25 ± 3	25 ± 3	25 ± 2	0.29
24 h Ambulatory BP	Systolic BP day time (mmHg)	142 ± 11	142 ± 12	143 ± 11	0.41
	Diastolic BP day time (mmHg)	93 ± 9	93 ± 9	93 ± 9	0.79
	Systolic BP night time (mmHg)	126 ± 13	126 ± 13	126 ± 13	0.77
	Diastolic BP night time (mmHg)	79 ± 11	79 ± 11	77 ± 11	0.17
Electrolytes and kidney function	U. Sodium (mEq/24h)	142 ± 70	144 ± 72	136 ± 63	0.17
	U. Potassium (mEq/24h)	60 ± 23	60 ± 23	61 ± 23	0.78
	eGFR (ml/min/1.73 m^2)	101 ± 13	101 ± 14	100 ± 13	0.41
	Pl. Sodium (mEq/L)	142± 2	142 ± 2	142 ± 3	0.25
	Pl. Potassium (mEq/L)	4.0 ± 0.4	4.0 ± 0.3	4.0 ± 0.4	0.81
RAAS and water balance	PRA (ng/mL/h)	1.9 ± 1.8	2.0 ± 2.0	1.7 ± 1.5	0.11
	Pl. Aldo (ng/dL)	171 ± 119	172 ± 121	170 ± 112	0.86
Klotho (n=243 NHPs)	α-Klotho (pg/mL)	832 ± 223	829 ± 230	838 ± 203	0.78

Normally distributed numerical data expressed as mean±SD; [a] Data presented as size and frequency N (%); F, Female; M, Male; NHPs, Naïve Hypertensive Patients, U., Urinary; PRA, plasma renin activity; Aldo, aldosterone.

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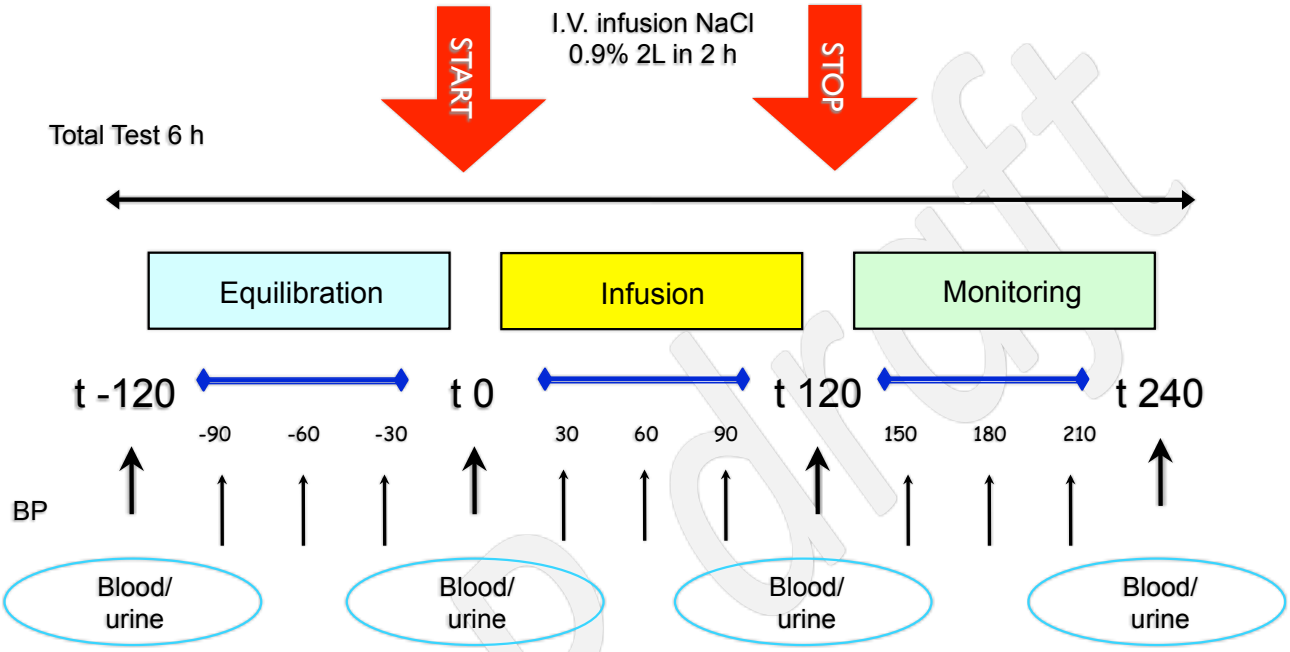
Supplemental Table 6. Baseline clinical characteristics of the replication naïve hypertensive cohort that underwent the acute saline load, and comparison with the discovery naïve hypertensive cohort.

	Parameters	Replication NHP cohort (n=193)	Discovery NHP cohort (n=673)	p ANOVA
Anthropometric	Age (years)	48 ± 9	45 ± 10	**<0.001**
	Sex (F/M) [a]	51 (26)/142 (74)	126 (19)/547 (81)	**0.01**
	BMI (kg/m^2)	26 ± 3	25 ± 3	**<0.001**
24 h Ambulatory BP	Systolic BP day time (mmHg)	142 ± 10	142 ± 11	0.91
	Diastolic BP day time (mmHg)	91 ± 8	93 ± 9	0.05
	Systolic BP night time (mmHg)	126 ± 13	126 ± 13	0.55
	Diastolic BP night time (mmHg)	76 ± 10	79 ± 11	0.07
Electrolytes and kidney function	U. Sodium (mEq/24h)	138 ± 64	142 ± 70	0.48
	U. Potassium (mEq/24h)	62 ± 23	60 ± 23	0.32
	eGFR (ml/min/1.73 m^2)	96 ± 13	101 ± 13	**<0.001**
	Pl. Sodium (mEq/L)	142 ± 2	142 ± 2	0.23
	Pl. Potassium (mEq/L)	4.0 ± 0.3	4.0 ± 0.4	0.10
RAAS and water balance	PRA (ng/mL/h)	NA	1.9 ± 1.8	-
	Pl. Aldo (ng/dL)	NA	171 ± 119	-
	Pl. Renin (µIU/mL)	8.9 ± 13	NA	-
	Pl. Aldo (pg/mL)	127 ± 87	NA	-

Normally distributed numerical data expressed as mean±SD; [a] Data presented as size and frequency N (%); F, Female; M, Male; SR, Salt Resistant; SS, Salt-Sensitive; NHPs, Naïve Hypertensive Patients; U., Urinary; PRA, plasma renin activity; Aldo, aldosterone; NA, Not Available

Supplemental Figure 1. Salt loading test scheme. The saline test was performed with intravenous infusion of 2L of 0.9% saline solution (=308 mmol Na+). Monitoring of BP was every 30 min while blood/urine collection was every 120 min.



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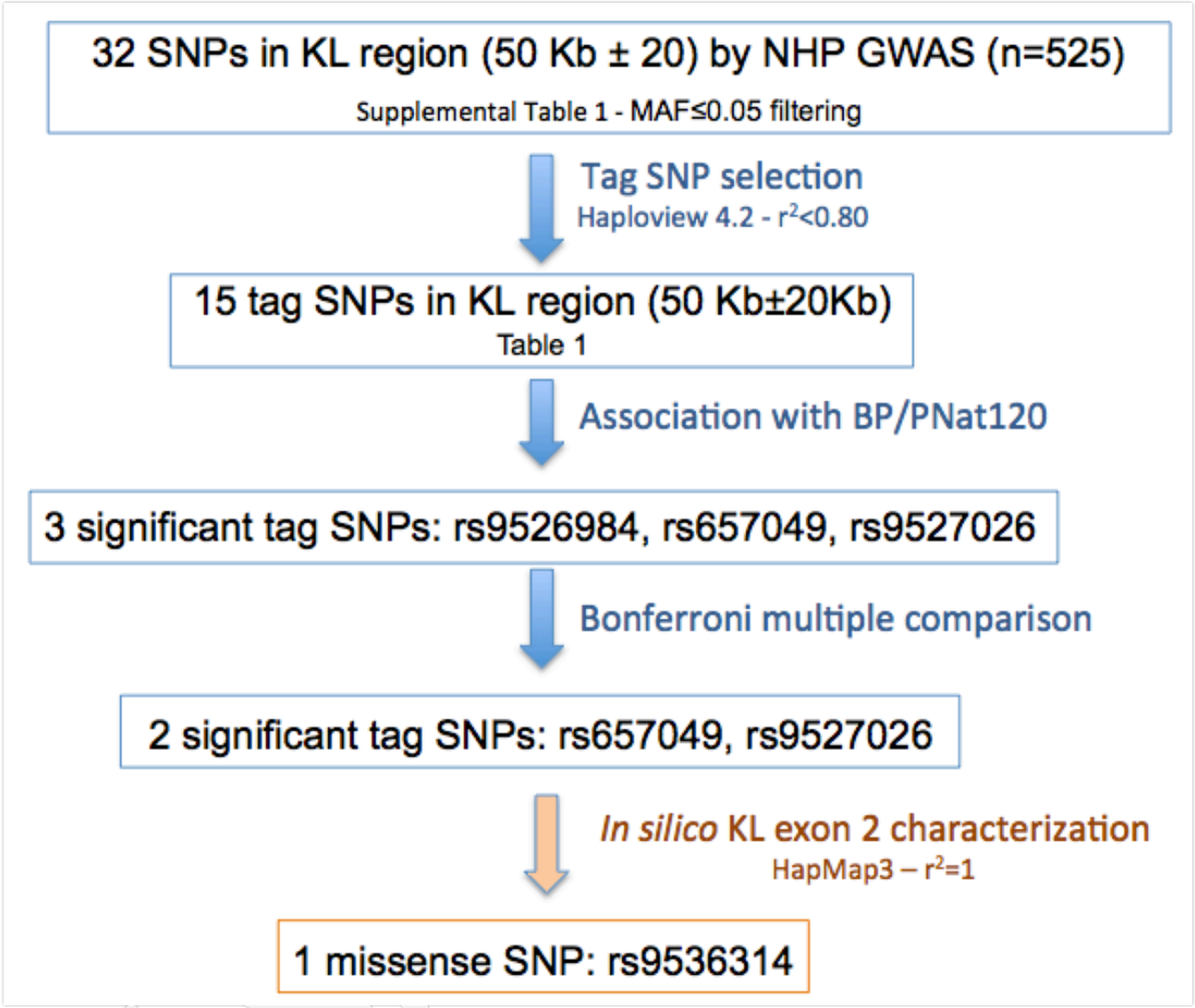
Supplemental Figure 2. Flow chart for the filtering of selected SNPs in KL region. NHP, naïve hypertensive patients; GWAS, genome-wide association study; PNat120, Pressure-Natriuresis at time 120.



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