

1 **Table 1.** Demographic and clinical characteristics of the study subjects

Parameter	Cases		Controls		P
	Mean (SD)	Min–Max	Mean (SD)	Min–Max	
<i>n</i>	311	–	286	–	–
Age (yr)	46.6 (9.0)	16–68	41.1 (8.1)	20–59	<0.0001
Duration of stay in NCR (yr)	39.0 (12.3)	7–68	33.1 (12.1)	10–59	<0.0001
Body mass index (kg/m ²)	21.1 (3.4)	13.6–35.7	23.0 (4.3)	15.6–43.7	<0.0001
Blood pressure (systolic) (mmHg)	124.0 (18.9)	65–220	128.0 (10.6)	90–139	0.0013
Blood pressure (diastolic) (mmHg)	71.0 (12.6)	35–125	74.6 (9.0)	47–89	<0.0001
Serum creatinine (mg/dL)	2.12 (1.10)	0.46–11.1	0.88 (0.11)	0.56–1.18	<0.0001
eGFR (mL/min/1.73 m ²)	45.7 (23.1)	5.3–204.3	104.0 (17.0)	67.4–180.9	<0.0001
Urinary alpha-1-microglobulin (mg/L)	65.9 (52.3)	0.1–410.7	1.6 (2.4)	0.1–13.8	<0.0001
Glycated hemoglobin (HbA1c %)	5.5 (0.6)	3.7–9.8*	5.4 (0.5)	2.9–6.5	0.0052
Serum fluoride (µg/L)	86.4 (51.6)	12.7–367	35.5 (16.2)	9.5–99.0	<0.0001

2 eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

3 *Six cases were diagnosed with diabetes after the diagnosis of CKDu.

4

5

6 **Table 2.** Multiple logistic analysis for selected demographic, life-style and past events

7

Parameter	Odds ratio (95% CI)	<i>P</i>
Farming vs. other occupations	9.17 (20.00–4.18)	<0.0001
Family history of CKDu	2.66 (4.15–1.70)	<0.0001
Tobacco chewing	2.59 (4.02–1.68)	<0.0001
History of snake bites	1.93 (3.16–1.18)	0.0093
History of malaria	1.31 (1.96–0.87)	0.1925
Smoking	1.25 (1.89–0.83)	0.2782
Betel chewing	1.38 (2.38–0.80)	0.2520

8 CI, confidence interval; CKDu, chronic kidney disease of unknown etiology.

9 **Table 3. Metal concentrations in urine**

Metal	Cases (µg/L) n= 301				Controls (µg/L) n= 276				P ^a value	P ^b value
	Mean(SD)	Geometric Mean	Min-Max	25%/50%/75%	Mean(SD)	Geometric Mean	Min-Max	25%/50%/75%		
Pb	0.94(0.89)	0.69	0.05-8.42	0.39/0.68/1.16	1.88(2.55)	1.45	0.21-31.8	0.96/1.43/2.23	<0.001*	<0.001*
Tl	0.18(0.19)	0.12	0-1.10	0.06/0.11/0.22	0.38(0.26)	0.30	0.01-1.73	0.2/0.32/0.49	<0.001*	<0.001*
Cs	3.09(2.77)	2.18	0.25-20.3	1.13/2.16/4.23	5.81(4.08)	4.57	0.14-23.6	2.92/4.87/6.99	<0.001*	<0.001*
Cd	0.47(0.78)	0.25	0.02-7.17	0.11/0.25/0.52	1.76(1.89)	0.78	0.03-8.24	0.23/0.78/3.1	<0.001*	<0.001*
Mo	55.6(48.9)	38.4	2.36-314	19.4/42.6/75.9	105(97.5)	73.7	4.62-972	39.3/80.8/141	<0.001*	<0.001*
Sr	132 (115)	94.4	8.74-650	55.4/97.3/172	247(163)	191	16.1-829	119/226/332	<0.001*	<0.001*
Rb	1380(1250)	1020	185-9860	575/1030/1780	2360(1620)	1900	130-9900	1270/1980/2810	<0.001*	<0.001*
Se	16.8(15.0)	11.5	0.37-101	6.11/12.8/22.5	29.8(20.0)	23.6	2.00-124	15.9/25.4/38.2	<0.001*	<0.001*
As	33.2(37.5)	20.3	1.49-259	10.2/21.8/40.6	44.4(43.5)	29.6	1.22-277	18.1/30.2/55.4	<0.001*	<0.001*
Zn	374(322)	279	36.2-2130	163/276/476	428(453)	304	24.6-4210	180/315/522	0.1	>0.10
Cu	16.2(15.5)	12.0	0.99-153	7.70/11.9/19.3	15.7(11.6)	12.7	1.41-116	8.39/13.1/19.9	0.628	>0.10
Ni	4.04(3.06)	3.11	0.18-23.2	1.79/3.18/5.27	5.52(4.19)	4.51	0.45-37.9	3.07/4.54/6.92	<0.001*	<0.001*
Co	0.42(0.41)	0.30	0.04-3.30	0.17/0.32/0.48	0.55(0.48)	0.42	0.03-3.28	0.26/0.42/0.65	<0.001*	<0.001*
Fe	10.8(24.4)	5.83	0.04-280	3.37/5.89/10.4	11.5(46.9)	6.82	1.36-773.18	4.3/6.59/9.86	0.817	<0.025
Mn	0.68(1.14)	0.51	0.07-19.0	0.34/0.53/0.75	0.84(1.97)	0.59	0.08-31.9	0.38/0.60/0.90	0.213	<0.05
Cr	0.19(0.30)	0.12	0-3.62	0.08/0.13/0.19	0.24(0.78)	0.15	0.01-12.63	0.10/0.15/0.23	0.291	<0.005
V	0.46(0.31)	0.36	0.02-1.66	0.24/0.41/0.61	0.67(0.31)	0.58	0.01-2.67	0.46/0.68/0.86	<0.001*	<0.001*
Al	4.60(3.61)	3.70	0.31-30.0	2.54/3.67/5.52	6.60(8.51)	4.95	0.03-114.98	3.37/4.78/7.39	<0.001*	<0.001*

10 P^a, P value calculated by t-test; P^b, P value calculated by Kolmogorov-Smirnov (non-parametric) test; *Significant by Bonferroni correction (p=0.05/18=0.003)

12 **Table 4.** As speciation results unadjusted and adjusted by urinary creatinine levels

Component	Controls (n=154)			Cases (n=176)			P ^a value	P ^b value
	mean (SD)	Min–Max	25%/50%/75%	mean (SD)	Min–Max	25%/50%/75%		
Unadjusted for creatinine								
As(III) (µg/L)	0.71(0.94)	<0.02–9.71	0.14/0.59/1.05	0.39(2.16)	<0.02–28.0	<0.02/0.10/0.27	0.095	<0.05
As(V) (µg/L)	0.22(0.36)	<0.02–3.42	0/0.14/0.27	0.14(0.24)	<0.02–2.42	<0.02/0.10/0.18	<0.05	>0.1
MMA (µg/L)	0.57(0.57)	<0.02–5.09	0.23/0.46/0.73	0.56(0.58)	<0.02–4.49	0.21/0.37/0.62	0.859	>0.1
DMA (µg/L)	7.83(7.75)	0.49–65.9	3.63/5.94/9.21	6.39(7.40)	0.41–46.4	2.16/4.60/7.19	0.087	<0.05
AB (µg/L)	33.0(35.7)	<0.02–215	10.0/20.5/41.0	25.5(33.4)	0.17–227	6.96/15.2/28.8	<0.05	<0.05
Total As (µg/L)	42.4(38.6)	1.62–237	16.5/29.4/52.5	33.0(37.8)	1.77–234	9.78/22.2/40.8	<0.05	<0.05
UCr (g/L)	1.19(0.7)	0.06–3.87	0.68/1.08/1.50	0.72(0.53)	0.06–4.11	0.34/0.59/0.97	<0.05	<0.05
Adjusted for creatinine								
As(III) (µg/g-Cr)	0.82(1.36)	ND–14.5	0.18/0.45/1.23	0.77(5.25)	ND–69.4	ND/0.18/0.42	0.404	<0.05
As(V) (µg/g-Cr)	0.28(0.52)	ND–5.12	ND/0.12/0.33	0.35(0.88)	ND–9.08	ND/0.14/0.34	<0.05	<0.1
MMA (µg/g-Cr)	0.54(0.40)	ND–2.60	0.3/0.48/0.68	0.92(0.67)	ND–3.91	0.47/0.72/1.19	<0.05	<0.05
DMA (µg/g-Cr)	7.05(6.02)	1.14–58.7	3.98/5.42/8.41	9.43(6.06)	1.52–35.5	5.44/7.97/11.8	<0.05	<0.05
AB (µg/g-Cr)	29.0(31.5)	ND–258	11.1/21.6/33.7	40.2(44.9)	1.08–275	13.4/24.5/45.9	<0.05	<0.10
Total As (µg/g-Cr)	37.7(32.7)	4.1–270	18.8/30.9/43.4	51.7(47.6)	6.04–303	21.1/36.2/59.2	0.095	<0.05

13 *Significant by Bonferroni correction

14 P^a, P value calculated by t- test; P^b, P value calculated by Kolmogorov-Smirnov (non-parametric) test

15 MMA, Monomethylarsonic acid; DMA, Dimethylarsinic acid; AB, Arsenobetaine; UCr, urinary creatinine; ND, not detected
16

Table 5. Ten SNPs with significant and suggestive evidence of associations identified in the genome-wide association study

SNP	Chr:position	Alleles	Gene	Distance	MAF (number)		Slope (OR)	P value for QTL analysis (dichotomous analysis)		
					Cases	Controls		Without age adjustment	With age adjustment	
1	rs17126268	1:102498987	T>C	<i>OLFM3</i>	264	0.03 (Wild=281, HT=19, Homo=1)	0.10 (Wild=225, HT=48, Homo=3)	17.42 (2.78)	7.19×10 ⁻⁷ (1.58×10 ⁻⁵)	5.29×10 ⁻⁶ (9.64×10 ⁻⁵)
2	rs7539242	1:102499390	G>A	<i>OLFM3</i>	264	0.03 (Wild=281, HT=19, Homo=1)	0.10 (Wild=225, HT=48, Homo=3)	17.42 (2.78)	7.19×10 ⁻⁷ (1.58×10 ⁻⁵)	5.29×10 ⁻⁶ (9.64×10 ⁻⁵)
3	rs12135261	1:102501863	C>T	<i>OLFM3</i>	266	0.03 (Wild=281, HT=19, Homo=1)	0.10 (Wild=225, HT=48, Homo=3)	17.42 (2.78)	7.19×10 ⁻⁷ (1.58×10 ⁻⁵)	5.29×10 ⁻⁶ (9.64×10 ⁻⁵)
4	rs12120258	1:102507539	G>T	<i>OLFM3</i>	272	0.03 (Wild=281, HT=19, Homo=1)	0.10 (Wild=225, HT=48, Homo=3)	17.42 (2.78)	7.19×10 ⁻⁷ (1.58×10 ⁻⁵)	5.29×10 ⁻⁶ (9.64×10 ⁻⁵)
5	rs12140211	1:102512105	C>T	<i>OLFM3</i>	276	0.07 (Wild=259, HT=41, Homo=1)	0.14 (Wild=203, HT=68, Homo=5)	13.71 (2.00)	9.54×10 ⁻⁷ (9.21×10 ⁻⁵)	1.48×10 ⁻⁵ (7.59×10 ⁻⁴)
6	rs2980098	4:4303857	A>G	<i>TMEM128</i>	13	0.37 (Wild=120, HT=138, Homo=43)	0.49 (Wild=73, HT=138, Homo=65)	9.11 (1.61)	3.80×10 ⁻⁶ (1.00×10 ⁻⁴)	2.16×10 ⁻⁶ (1.22×10 ⁻⁴)
7	rs10099338	8:9295149	A>G	<i>LOC157273</i>	65	0.05 (Wild=273, HT=28, Homo=0)	0.10 (Wild=221, HT=53, Homo=2)	13.28 (2.04)	4.05×10 ⁻⁶ (1.00×10 ⁻⁴)	4.50×10 ⁻⁴ (4.33×10 ⁻³)
8	rs1004571	20:44711576	A>G	<i>SLC13A3</i>	Intragenic	0.32 (Wild=32, HT=129, Homo=140)	0.44 (Wild=51, HT=142, Homo=83)	7.98 (1.63)	4.33×10 ⁻⁶ (2.78×10 ⁻⁵)	6.23×10 ⁻⁵ (1.73×10 ⁻⁴)
9	rs6066043	20:44721860	G>A	<i>SLC13A3</i>	Intragenic	0.23 (Wild=175, HT=113, Homo=13)	0.38 (Wild=104, HT=132, Homo=40)	12.17 (2.13)	2.40×10 ⁻⁹ (1.13×10 ⁻⁸)	5.23×10 ⁻⁹ (3.73×10 ⁻⁸)
10	rs4810537	20:44740335	A>G	<i>SLC13A3</i>	Intragenic	0.33 (Wild=32, HT=137, Homo=132)	0.45 (Wild=54, HT=142, Homo=80)	8.02 (1.60)	3.47×10 ⁻⁶ (2.78×10 ⁻⁵)	6.08×10 ⁻⁵ (2.67×10 ⁻⁴)

- 18 Chr, chromosome; MAF, minor allele frequency; OR, odds ratio; HT, heterozygous; SNP, single nucleotide polymorphism; QTL, quantitative trait locus.
- 19 P values for both the QTL analysis and dichotomous analysis are shown.
- 20 Reference sequence: GRCh36 (2006)

1 **Table S1. Univariate logistic analyses for demographic factors, lifestyle, medical**

2 **history, and family history of the study subjects**

Parameter	Cases Frequency (%)	Controls Frequency (%)	Odds ratio	<i>P</i>
Farming vs. other occupations	302 (97.11)	200 (69.93)	12.66	<0.0001
History of malaria	201 (64.63)	142 (49.65)	1.85	0.0002
History of leptospirosis	4 (1.29)	2 (0.7)	1.85	0.4798
History of snakebites	83 (26.69)	36 (12.59)	2.50	<0.0001
Smoking	205 (66.6)	151 (52.8)	1.79	0.0007
Alcohol consumption	207 (67.4)	197 (69.1)	0.93	0.6583
Betel chewing	247 (80.46)	184 (64.34)	2.28	<0.0001
Tobacco chewing	151 (54.51)	72 (26.77)	3.22	<0.0001
Family history of hypertension	140 (45.02)	135 (47.20)	0.91	0.5927
Family history of diabetes	51 (16.4)	65 (22.73)	0.67	0.0519
Family history of CKDu	122 (39.23)	50 (17.48)	3.03	<0.0001

3 CKDu, chronic kidney disease of unknown etiology.

4

5

6 **Table S2.** Metal concentrations in drinking water

Element	Min	Max	AM (ASD)	Median	GM (GSD)	Drinking water standard, maximum allowable limit		Japan's standard ^c
						Primary	Secondary	-
Na (mg/L)	5.53	134	54.5 (36.2)	49.7	39.9 (2.51)	-	200 ^b	-
Mg (mg/L)	4.38	56.6	21.0 (14.6)	18.0	16.6 (2.05)	-	-	-
K (mg/L)	0.180	7.99	1.13 (1.45)	0.660	0.771 (2.22)	-	-	-
Ca (mg/L)	9.02	90.2	26.5 (16.7)	22.1	22.9 (1.71)	-	-	-
Al (µg/L)	0.050	7.40	0.681 (1.43)	0.200	0.239 (3.81)	-	200 ^a	-
Cr (µg/L)	0.010	0.208	0.040 (0.043)	0.027	0.029 (2.10)	50 ^b	-	-
Mn (µg/L)	0.044	3.14	0.669 (0.746)	0.372	0.407 (2.77)	400 ^b	50 ^a	≤200
Co (µg/L)	0.010	0.087	0.024 (0.016)	0.022	0.021 (1.69)	-	-	-
Ni (µg/L)	0.040	32.5	1.56 (5.78)	0.270	0.376 (3.47)	70 ^b	-	-
Cu (µg/L)	0.090	30.4	1.31 (5.40)	0.300	0.329 (2.84)	-	2000 ^b	-
Zn (µg/L)	0.005	27.7	1.63 (4.93)	0.430	0.409 (4.91)	-	5000 ^b	-
As (µg/L)	0.060	1.94	0.245 (0.337)	0.130	0.170 (2.09)	10 ^{a,b}	-	≤10
Se (µg/L)	0.010	1.14	0.213 (0.257)	0.120	0.110 (3.37)	40 ^b	-	≤10
Rb (µg/L)	0.160	4.56	1.132 (0.974)	0.760	0.826 (2.25)	-	-	-
Sr (µg/L)	20.0	1230	251 (259)	184	159 (2.72)	4000 ^a	-	-
Cd (µg/L)	0.001	0.032	0.002 (0.006)	0.001	0.001 (2.25)	3 ^b	-	≤10
Ba (µg/L)	8.90	171	71.1 (53.9)	52.4	49.4 (2.56)	700 ^b	-	-
Pb (µg/L)	0.001	0.125	0.007 (0.023)	0.001	0.002 (3.42)	10 ^b	-	≤10
U (µg/L)	0.003	0.341	0.060 (0.079)	0.027	0.031 (3.38)	30 ^b	-	≤2

7 ^aUnited States Environmental Protection Agency (US EPA) drinking water guidelines (<http://water.epa.gov/drink/contaminants/index.cfm>).

- 8 ^bWHO guidelines for drinking-water quality, 4th edition (2011)
9 (http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/index.html).
- 10 ^cMOE Japan, Ministry of Environment, Japan (2004). Environment Quality Standards for Water Pollution
11 (<http://www.env.go.jp/en/water/wq/wp.pdf>).
- 12 AM, arithmetic mean; ASD, arithmetic standard deviation; GM, geometric mean; GSD, geometric standard deviation.
13

13 **Table S3.** Metal concentrations in urine

Metal	Cases (µg/g-Cr) n= 301				Controls (µg/g-Cr) n = 276				P ^a value	P ^b value
	Mean(SD)	Geometric Mean	Min-Max	25%/50%/75%	Mean(SD)	Geometric Mean	Min-Max	25%/50%/75%		
Pb	1.54(1.23)	1.26	0.28-11.3	0.8/1.17/1.81	1.74(1.77)	1.44	0.41-19.7	1.01/1.36/1.91	0.102	<0.001*
Tl	0.27(0.20)	0.21	0.02-1.74	0.14/0.21/0.34	0.33(0.18)	0.30	0.09-1.20	0.22/0.29/0.39	<0.001*	<0.001*
Cs	4.71(2.93)	3.93	0.65-16.4	2.42/4.22/5.94	5.01(2.08)	4.57	0.93-12.1	3.44/4.89/6.19	0.163	<0.001*
Cd	0.68(1.17)	0.45	0.04-15.5	0.27/0.45/0.7	2.03(3.47)	0.78	0.04-32.3	0.25/0.58/2.55	<0.001*	<0.001*
Mo	89.3(66.3)	69.3	3.97-457	43.2/70.7/119.2	92.9(72.3)	73.6	9.80-529	46.8/76.3/112	0.542	>0.1
Sr	208(148)	171	22.4-1130	110/174/256	223(121)	190	13.2-593	133/195/301	0.167	<0.05
Rb	2050(1050)	1840	673-8440	1360/1810/2590	2100(962)	1900	529-7160	1420/1930/2520	0.587	>0.1
Se	23.7(13.6)	20.5	0.41-111	16.1/20.9/28.6	24.9(8.57)	23.6	7.32-64.8	19.2/24.0/28.9	0.192	<0.001*
As	50.3(46.3)	36.8	5.13-320	20.8/36.3/60.6	39.4(34.9)	29.6	2.47-288	18.1/29.8/45.9	0.002	<0.005
Zn	571(306)	504	92.6-2130	376/496/712	359(255)	303	57.1-2870	213/308/424	<0.001*	<0.001*
Cu	26.4(20.9)	21.6	2.96-185	14.3/21.0/30.2	13.9(7.03)	12.7	5.88-61.2	9.46/12.0/15.5	<0.001*	<0.001*
Ni	6.91(5.58)	5.62	0.41-57.8	3.80/5.42/8.03	5.81(7.97)	4.51	1.04-96.1	3.17/4.23/5.95	0.054	<0.001*
Co	0.64(0.48)	0.54	0.15-3.64	0.36/0.51/0.76	0.49(0.52)	0.42	0.15-7.87	0.30/0.40/0.55	<0.001*	<0.001*
Fe	16.9(25.3)	10.5	0.09-295	5.96/10.5/18.3	10.3(32.6)	6.82	2.46-527	4.41/6.21/9.06	0.006	<0.001*
Mn	1.27(1.33)	0.92	0.1-11.6	0.56/0.85/1.42	0.88(1.6)	0.59	0.10-21.8	0.35/0.59/0.93	0.001*	<0.001*
Cr	0.47(2.09)	0.22	0-34.87	0.12/0.22/0.38	0.27(0.81)	0.15	0.03-8.61	0.10/0.14/0.21	0.128	<0.001*
V	0.88(0.87)	0.65	0.05-5.89	0.38/0.61/0.94	0.67(0.39)	0.58	0.06-3.01	0.41/0.58/0.79	<0.001*	<0.1
Al	9.29(10.22)	6.67	0.83-87.1	4.21/6.29/10.3	6.52(6.79)	4.95	0.13-67.5	3.33/4.57/7.29	<0.001*	<0.001*

14 P^a, P value calculated with t-test; P^b, P value calculated with Kolmogorov-Smirnov (non-parametric) test. *Significant by Bonferroni
 15 correction (p=0.05/18=0.003).

16 **Table S4.** Analysis of serum Fluoride levels among the subjects stratified according to the
 17 eGFR levels.
 18

Group	Serum Fluoride parameter	Controls	CKDu Cases	P value (Kolmogorov-Smirnov Test)
eGFR* >90 CKD stage 0 and 1	Median (µg/L)	30.9	29.6	P > 0.10
	GM (µg/L)	30.4	34.8	
	75% (µg/L)	40.0	48.9	
	25% (µg/L)	22.1	25.2	
	No of readings	209	9	
60<eGFR* <90 CKD stage 2	Median (µg/L)	37.8	40.9	P > 0.10
	GM (µg/L)	38.8	45.4	
	75% (µg/L)	49.4	69.6	
	25% (µg/L)	31.8	30.9	
	No of readings	56	57	

19 All the subjects with eGFR<60 mL/min/1.73m² were eliminated due to unavailability of controls in
 20 this range. Serum fluoride levels were not normally distributed within the groups and we used a
 21 non-parametric method (Kolmogorov-Smirnov Test) to evaluate the difference statistically. * Unit for
 22 eGFR- mL/min/1.73m²

Table S5. Results of direct sequencing of SLC13A3 and TP53RK

Position in Chr 20	rs	SNPs	Wild	G/case11	G/case30	G/case15	G/case119	M/case49	M/case150	M/case9	M/case111	Minor allele count in Cases	MAF in Cases ^{a)}	G/con69	G/con168	G/con143	G/con153	M/con129	M/con73	M/con76	M/con152	MA count in Controls	MAF in Controls ^{a)}	Fisher exact test ^{b)}	
SLC13A3																									
45296512	-	IVS2+2170	CC	CC	CC	CT	CC	CC	CC	CC	CC	1	0.06	CC	CC	CC	CC	CC	CC	CC	CC	CC	0	0	
45295394	rs149153771	IVS2+3288	GG	GA	GG	GG	GG	GG	GG	GG	GG	1	0.06	GG	GG	GG	GG	GG	GG	GG	GG	GG	0	0	
45295154	rs11469962	IVS2+3526	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)14/(CAA)14/	(CAA)15/(CAA)15/	(CAA)14/(CAA)14/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	9	0.64	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	(CAA)15/(CAA)15/	2	0.14	**
45295156	-	IVS2+3526	CAA)15	CAA)15	CAA)14	CAA)14	CAA)14	CAA)14	CAA)14	CAA)13	CAA)14	1	0.06	CC	CT	CC	CC	CC	CC	CC	CC	CC	1	0.06	
45281710	rs191701536	IVS2-1610	CC	CC	CC	CT	CC	CC	CC	CC	CC	1	0.06	TT	TT	TT	TT	TT	TT	TT	TT	TT	0	0	
45281673	rs188451937	IVS2-1573	TT	CT	TT	TT	TT	TT	TT	TT	TT	1	0.06	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	3	0.19	
45281595	rs34571845	IVS2-1495	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	CA/CA	4	0.25	CC	CC	CC	CC	CC	CC	CC	CC	CC	0	0	
45281276	-	IVS2-1176	CC	CC	CC	CC	CT	CC	CC	CC	CC	1	0.06	CG	CG	CC	CG	CG	CG	CG	CG	CG	6	0.38	
45242269	rs2273024	p.L69L	CC	CG	CC	CG	CG	CC	CC	CC	CC	3	0.19	GT	GT	GG	GT	GT	GT	GT	GT	GT	6	0.38	
45237244	rs3764693	IVS6+104	GG	GT	GG	GT	GG	GG	GG	GG	GG	3	0.19	CC	CC	CC	CC	CC	CC	CC	CC	CC	0	0	
45220994	-	IVS9+49	CC	CC	CC	CC	CT	CC	CC	CC	CC	1	0.06	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	3	0.19	
45220868	rs 142792823		(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	2	0.13	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	(TATG)6/(TATG)6/	3	0.19	
45216526	-	IVS11+172	TT	GG	TT	GG	GG	GG	GG	GG	GG	14	0.88	GG	GG	GG	GG	TT	TT	GG	GG	TT	12	0.75	
45214052	rs12625158	IVS11-12	GG	GA	GG	GA	GG	GG	GA	GG	GG	3	0.19	GG	GG	GG	GA	GG	GG	GG	GG	GG	1	0.06	
45213435	rs76086573	UTR	TT	TT	TT	TT	TG	TT	TT	TT	TT	1	0.06	TT	TT	TT	TT	TT	TT	TT	TT	TT	0	0	
45212754	-	UTR	AA	AA	AA	AA	AA	AA	AA	AA	AA	0	0	AA	AA	AA	AA	AA	AA	AA	AA	AA	1	0.06	
45212620	rs863675	UTR	TT	TT	TT	TT	TT	TT	TT	CT	TT	1	0.06	TT	TT	TT	TT	TT	TT	CC	TT	TT	2	0.13	
45212455	rs389905	UTR	TT	TG	TT	TG	TT	TT	TG	TG	TT	4	0.25	TT	TT	TT	TG	TT	TT	GG	TT	TT	3	0.19	
45212236	-	UTR	CC	CC	CC	CC	CC	CC	CC	CC	CC	0	0	CC	CG	CC	CC	CG	CC	CC	CC	2	0.13		
45211982	-	UTR	TT	TT	TT	TC	TT	TT	TT	TT	TT	1	0.06	TT	TT	TT	TT	TT	TT	TT	TT	TT	0	0	
45211549	rs2064342	UTR	TT	TC	TT	TC	TC	TT	TC	TC	TT	5	0.31	TT	TC	TC	TC	TC	TT	CC	TT	CC	6	0.38	
45211090	rs111962970	UTR	TT	TA	TT	TA	TT	TT	TA	TA	TT	4	0.25	TT	TT	TT	TA	TT	TT	AA	TT	AA	3	0.19	
45212126	-	UTR	CC	CC	CC	CC	CC	CC	CC	CC	CC	0	0	CC	CG	CC	CC	CG	CC	CC	CC	2	0.13		
45204266	rs1880898	p.P426P	CC	CT	CT	TT	TT	TT	TT	TT	CC	12	0.75	CT	TT	CT	CT	CC	TT	TT	CT	TT	10	0.63	
45195518	rs56914549	IVS13-204	CC	CT	CT	CC	CC	CC	CC	CC	CC	2	0.13	CC	CT	CT	CC	CC	CT	CC	CT	CC	4	0.25	
45195407	rs202392	IVS13-93	TT	CC	TC	CC	CC	CC	CC	CC	TT	13	0.81	TC	TC	TC	TC	TT	CC	CC	TC	CC	9	0.56	
45195274	rs56923216	UTR	GG	GT	GG	GG	TT	GG	GG	GG	GG	2	0.14	GG	GT	GT	GG	GG	GT	GG	GT	GG	4	0.25	
45194904	rs202391	p.A486A	GG	CC	GG	GG	GG	GG	GG	GG	GG	2	0.13	GC	GG	GG	GG	GG	GG	GG	GG	GG	1	0.06	
45192420	-	IVS14-80	TT	TG	TT	TT	TG	TT	TT	TT	TT	2	0.14	TT	TT	TT	TT	TT	TT	TT	TT	TT	0	0	
45192377	rs847064	IVS14-37	AA	AG	GG	GG	GG	GG	GG	GG	AG	14	0.88	GG	GG	AG	GG	GG	GG	GG	GG	GG	15	0.94	
45192271	rs71183205	UTR	No	No ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	14	0.875	ins/ins	ins/ins	No ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	15	0.94	
45192272	-		insAGAG	AGAG/No	insAGAG	AGAG																			
45192254	rs74627632	UTR	CC	CT	TT	TT	TT	TT	TT	TT	CT	14	0.88	TT	TT	CT	TT	TT	TT	TT	TT	TT	15	0.94	
45188884	rs910061	IVS15-47	TT	TT	TC	TT	TT	TT	TT	TT	CC	3	0.19	TT	TC	TT	TC	TC	TT	TT	TC	TC	4	0.25	
45188433	rs4809591	3'UTR	GG	GG	GT	GG	GG	GG	GG	GG	TT	3	0.19	GG	GT	GG	GT	GT	GG	GG	GT	GG	4	0.25	
45187619	-	3'UTR	GG	GG	GG	GG	GA	GG	GG	GG	GG	1	0.06	GG	GG	GG	GG	GG	GG	GG	GG	GG	0	0	
45187565	-	3'UTR	AA	AA	AG	AA	AA	AA	AA	AA	AA	1	0.06	AA	AA	AA	AA	AA	AA	AA	AA	AA	0	0	
45187505	rs10218	3'UTR	GG	GG	GG	TT	TT	TT	TT	TT	GG	10	0.63	GT	GG	GG	GT	GT	TT	GG	GG	GG	6	0.38	
45187241	rs8149	3'UTR	TT	TC	CC	CC	CC	CC	CC	CC	CC	15	0.94	TC	CC	TC	CC	CC	CC	CC	CC	CC	14	0.88	
45186924	-	3'UTR	AA	AA	AA	AA	AA	AA	AA	AA	AA	1	0.07	AC	AA	AA	AA	AA	AA	AA	AA	AA	1	0.06	
45186748	rs12617	3'UTR	AA	AT	TT	TT	TT	TT	TT	TT	TT	15	0.94	AT	TT	AT	TT	TT	TT	TT	TT	TT	14	0.88	
45186736	rs3092272	3'UTR	No	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	16	1	ins/ins	ins/ins	No	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	ins/ins	14	0.88	
			insACTA/	No	insACTA											insACTA/	ins								
45186397	rs430114	3' near gene	AA	GG	GG	GG	GG	GG	GG	GG	GG	16	1	GG	GG	AG	GG	GG	GG	GG	GG	GG	15	0.94	
TP53RK																									
45318069	rs2664574	5'UTR	GG	GC	GG	GG	GG	GC	GG	GC	GC	3	0.21	GG	GG	GG	GG	GC	GC	GG	GC	GC	3	0.19	
45318042	rs2664523	p.A4A	CC	CT	CC	CC	CC	CC	CT	CC	CT	3	0.21	CC	CC	CC	CC	CT	CT	CC	CT	CC	3	0.19	
45315786	rs34983477	p.R123Q	GG	GG	GG	GG	GG	GG	GG	GG	GG	0	0	GG	GG	GG	GA	GG	GG	GG	GG	GG	1	0.06	
45314435	rs72485816	3' UTR	AA	AA	AA	AA	AA	AA	AA	AA	AG	2	0.13	AA	AA	AA	AA	AA	AA	AA	AA	AA	1	0.06	

a) MAF: Minor allele frequency
b) * p<0.05 and ** p<0.01

23 **Table S6.** Distribution of cases and controls among various CAA repeat combinations

24

CAA repeats	Cases		Controls	
	No	eGFR-Mean(SD)	No	eGFR-Mean(SD)
15/15	78	48.9 ^A (24.5)	111	105.6 ^B (15.0)
15/other	162	44.1 ^A (20.2)	131	104.0 ^B (19.0)
Other/other	61	45.0 ^A (28.1)	34	106.8 ^B (15.5)
Total	301	45.5(23.1)	276	104.1(17.1)

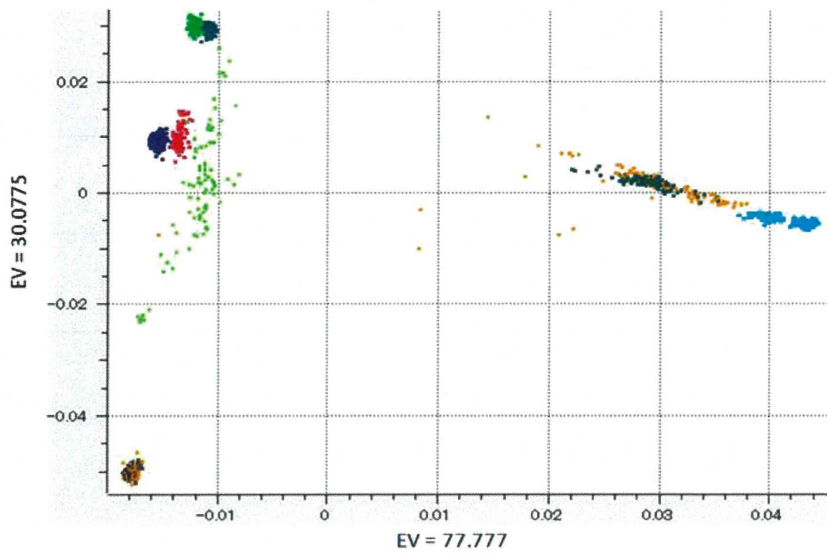
Odds ratio for other repeat number alleles against the 15 repeat allele: 1.6 (CI 1.3–2.1, P=8.4*10⁻⁵)

25

26 ANOVA was conducted within cases or controls. The same superscript letters indicate that there is
 27 no significant difference among CAA repeat combinations. An association study was conducted for
 28 the repeat number alleles, 15 repeats and others for CKDu. CI, confidence interval.

29

30



HapMap Data - ■ Utah residents with Northern and Western European ancestry ■ Han Chinese in Beijing, ■ Japanese in Tokyo ■ Yoruba in Nigeria ■ African ancestry in Southwest USA ■ Chinese in Colorado ■ Gujarati Indians in Texas ■ Luhya in Kenya ■ Mexican ancestry in California ■ Maasai in Kenya ■ Toscani in Italia

This project - ■ Sinhalese in Sri Lanka

Figure S1. Principal Component Analysis (PCA) of the cases and controls with other populations

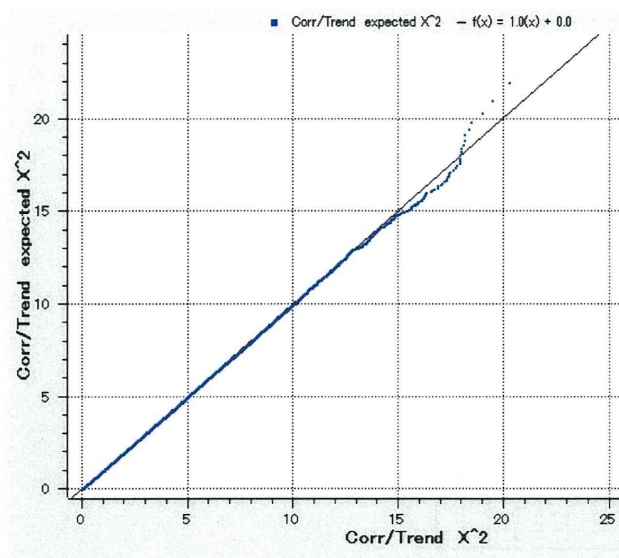


Figure S2. Q-Q plot.

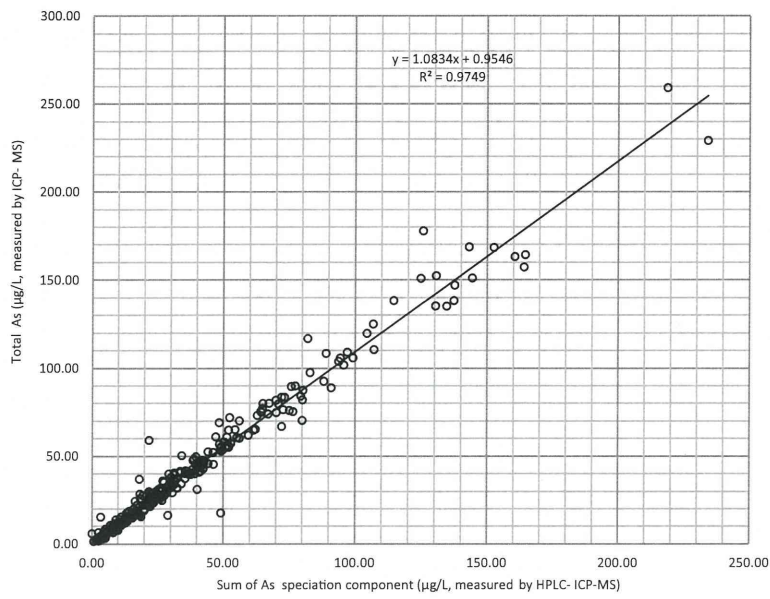


Figure S3. Comparison of total As levels measured by two different methodologies. As speciation and As determination by ICP-MS were conducted for 154 controls and 176 cases. The total As shown in Table 3 (Y) is plotted against total As shown in Table 4 (X). R was significant ($p < 0.001$).

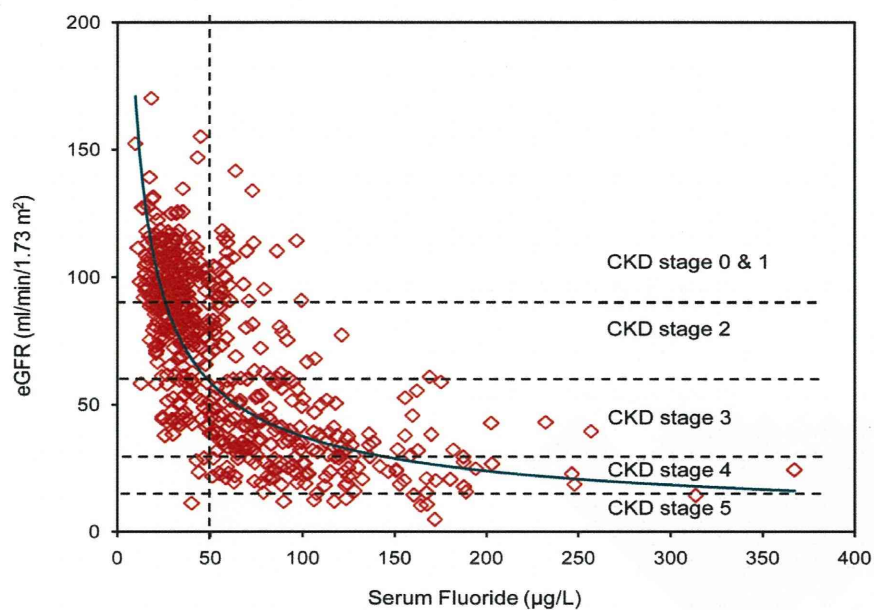


Figure S4. Variation of serum fluoride with eGFR level and CKD stage. Scattered plots of serum fluoride levels (X) and eGFR values (Y) for cases (n=301) and controls (N=276) are shown. 265 controls (96%) and 66 cases (22%) had eGFR greater than 60 ml/min/1.73 m².

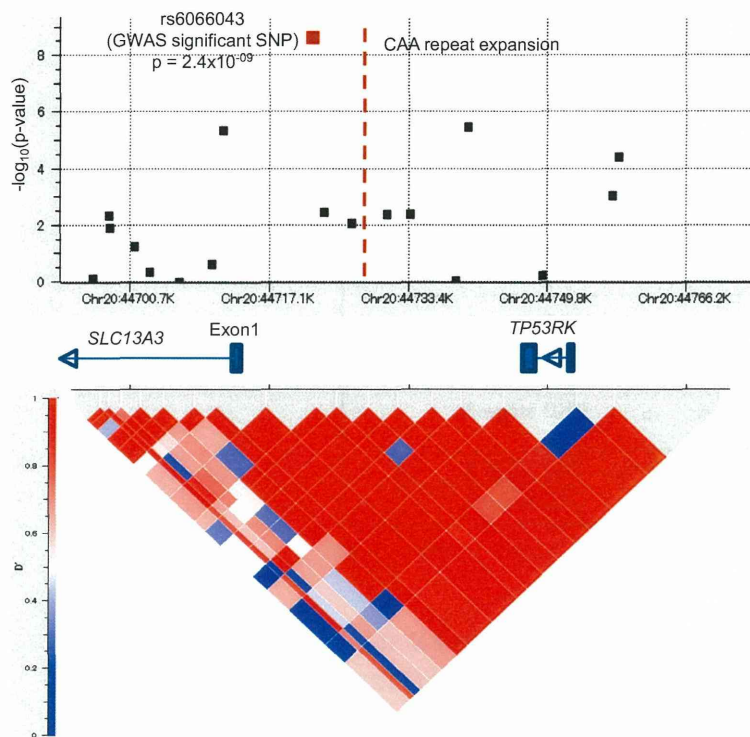


Figure S5. Linkage Disequilibrium block and position of the *SLC13A3* gene (NM_022829.5), GWAS significant SNP and CAA repeat (Chr20: 44630 – 44767 kbp in NCBI36/hg18). D' (D prime) represents strength of linkage disequilibrium. The $(CAA)_n$ repeat was located in the intergene region between *SLC13A3* and *TP53RK*.