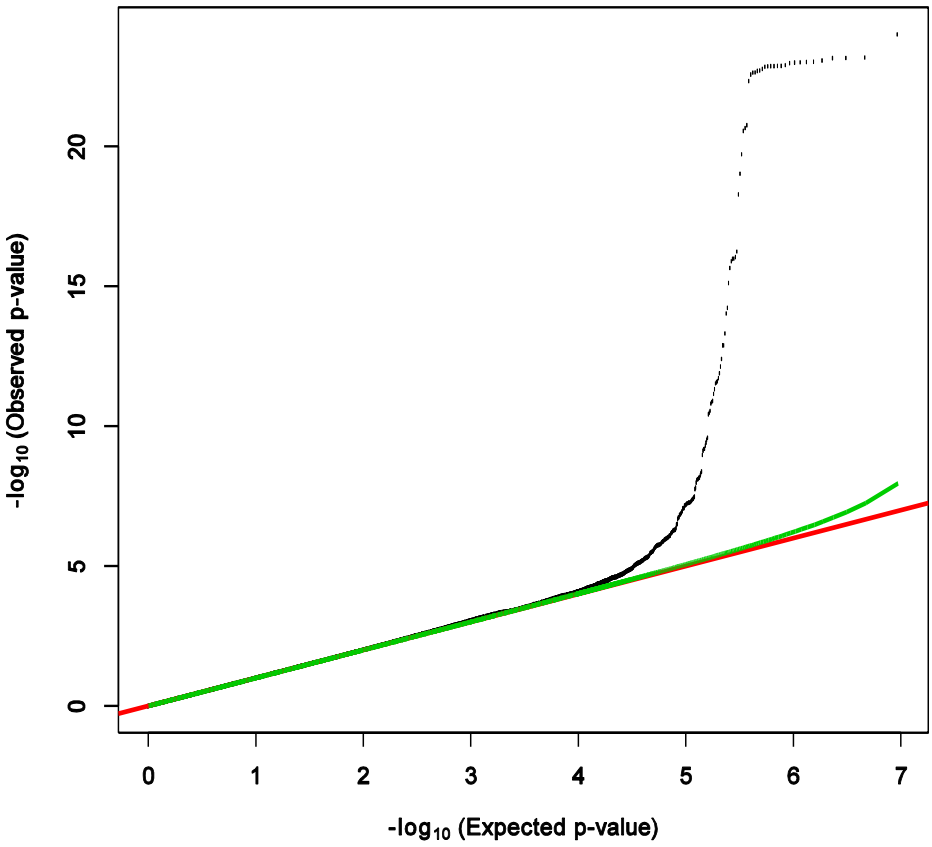
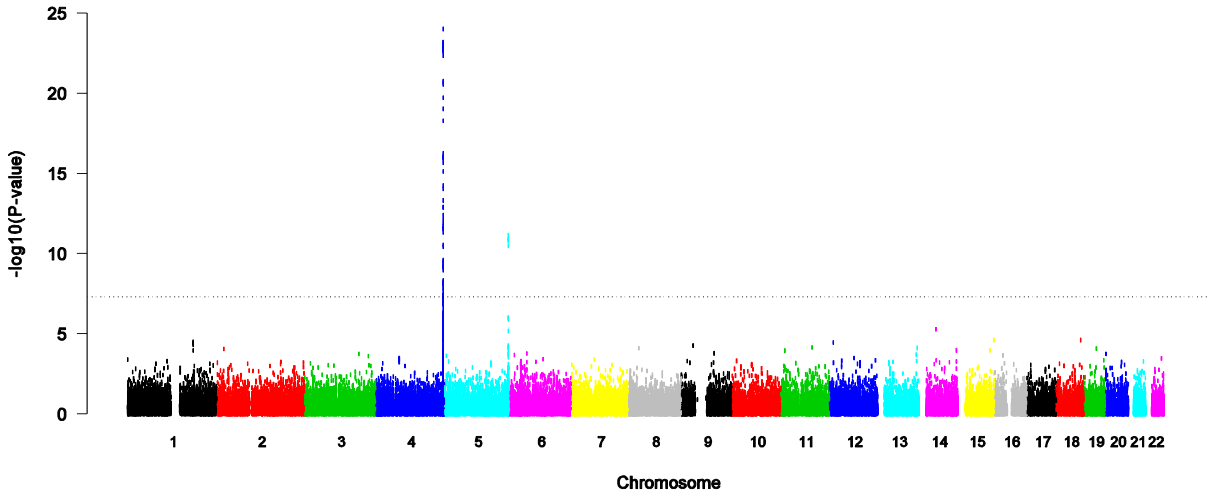
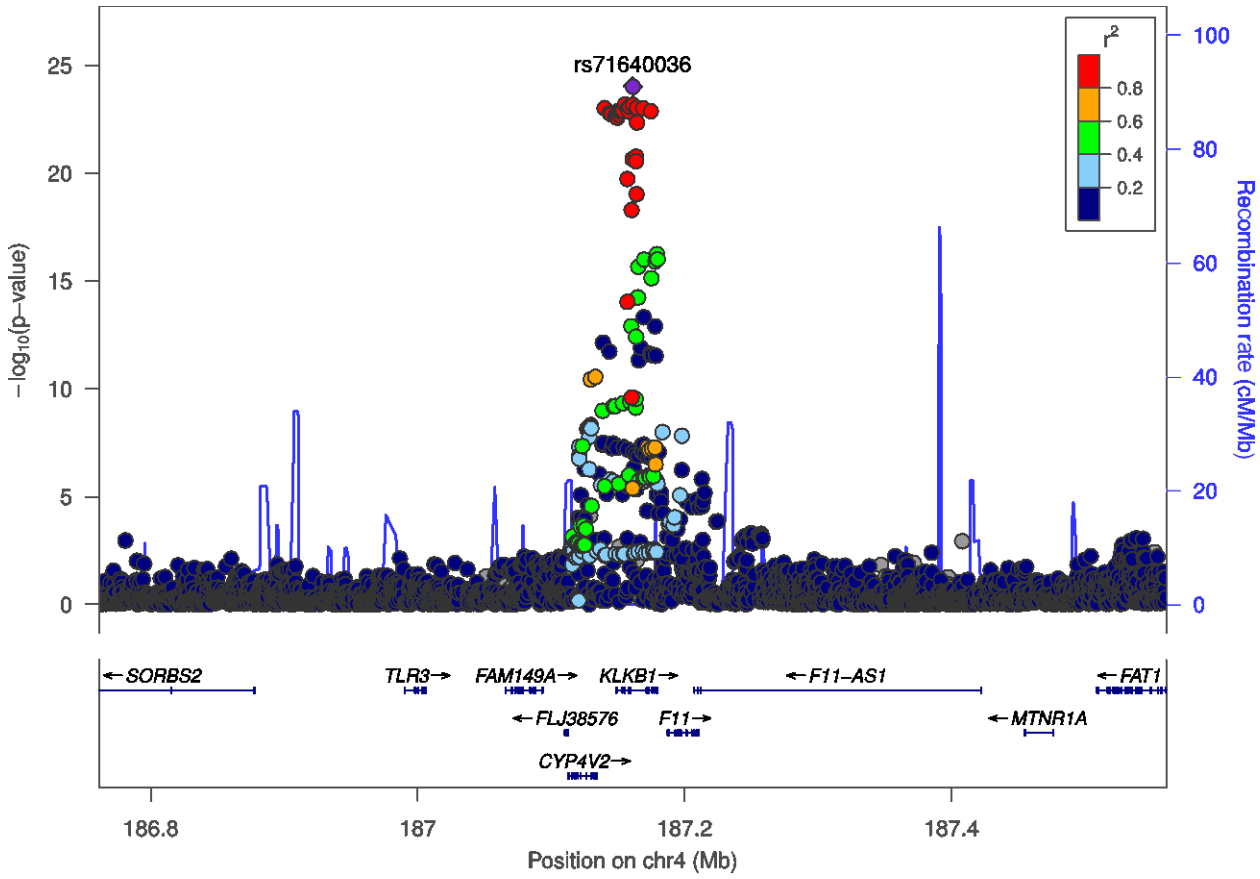
Supplementary Material to Zhang et al. “A genome-wide association study identifies genes in the kallikrein-kinin system associated with serum L-arginine levels” (Thromb Haemost 2016; 116.6)



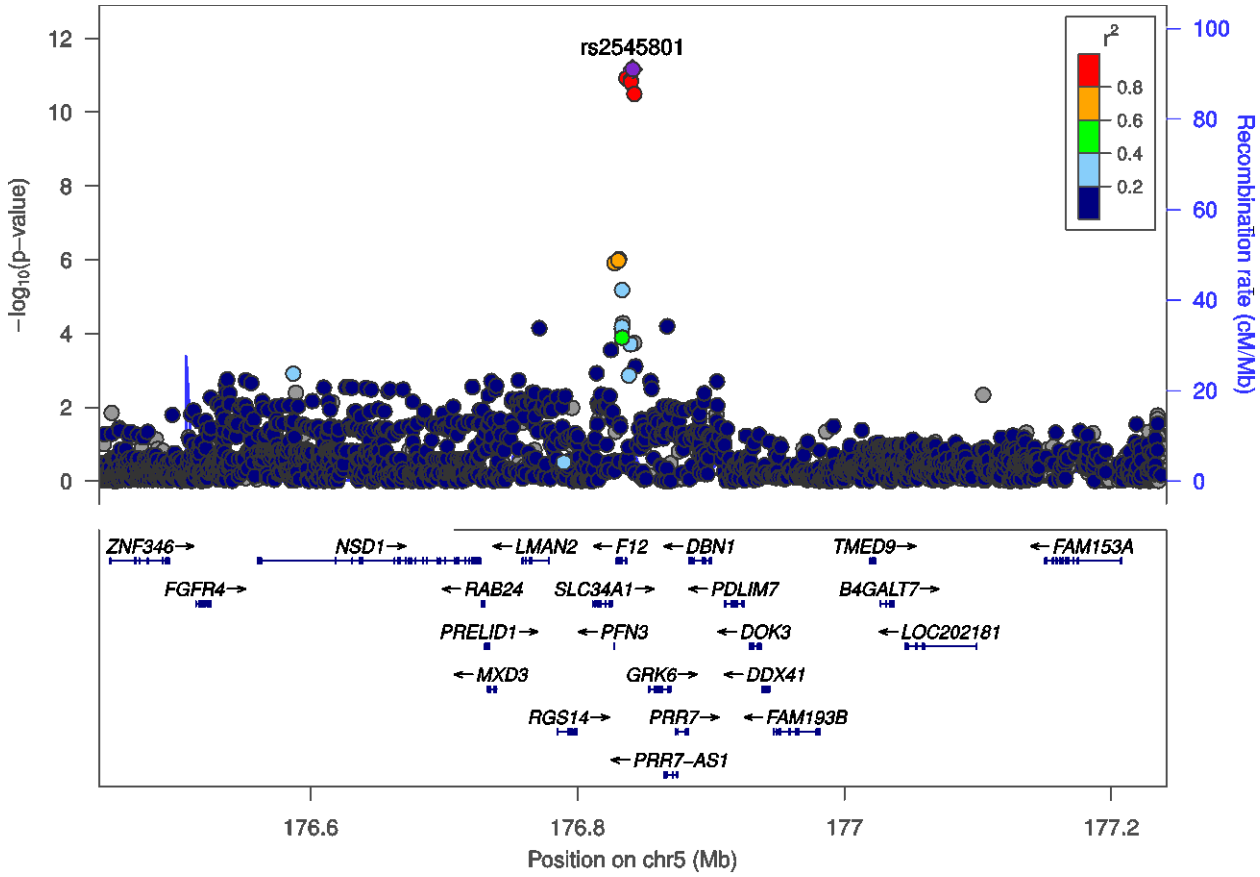
Suppl. Figure 1. Quantile-quantile (QQ) plot of combined GWAS results of serum L-arginine levels. The black dot represents observed association for each variant. The red line is expected under the null hypothesis of no association and the green curve is its 90% confidence interval upper limit.



Suppl. Figure 2. Manhattan plot of results for GWAS of serum L-arginine levels, dotted line indicates the genome-wide significance threshold ($p<5\times10^{-8}$).



Suppl. Figure 3. Regional plot of associations at the *KLKB1* locus.



Suppl. Figure 4. Regional plot of associations at the *F12* locus.

Suppl. Table 1. Association of serum L-arginine with clinical characteristics in the discovery cohorts. Results are shown as the change in L-arginine concentration (effect and standard error) associated with the clinical characteristic by linear regression analysis (adjusted for age, gender and ethnicity).

Trait	Effect	SE	P
Current smoking (yes vs no)	4.7	2.1	2.9×10^{-2}
Alcohol drinking (yes vs no)	-0.5	1.5	7.6×10^{-1}
Type 2 diabetes (yes vs no)	-7.0	1.9	1.9×10^{-4}
Coronary heart disease (yes vs no)	-6.5	3.2	4.1×10^{-2}
Hypertension (yes vs no)	1.7	1.4	2.3×10^{-1}
Body mass index (kg/m^2)	0.4	0.1	1.2×10^{-2}
Waist hip ratio	21.6	9.4	2.2×10^{-2}
Diastolic blood pressure (mmHg)	0.21	0.07	1.3×10^{-3}
Systolic blood pressure (mmHg)	0.10	0.04	1.0×10^{-2}
Cholesterol (mmol/L)	5.0	0.6	9.6×10^{-16}
Triglycerides (mmol/ L)	6.8	1.3	8.6×10^{-8}
LDL cholesterol (mmol/L)	5.7	0.7	2.3×10^{-14}
HDL cholesterol (mmol/ L)	1.2	2.1	5.6×10^{-1}
Glucose (mmol/L)	-7.9	2.9	6.1×10^{-3}
Insulin (IU/L)	3.5	0.9	1.1×10^{-4}
HbA1c (%)	-0.6	4.3	8.8×10^{-1}
HOMA-IR	2.2	0.8	7.7×10^{-3}
High-sensitive C-reactive protein (mg/L)	4.8	0.5	$< 2 \times 10^{-16}$
Creatinine (µmol/L)	6.0	4.5	1.8×10^{-1}

Footnotes: Triglycerides, glucose, insulin, HOMA-IR, HbA1c, High-sensitive C-reactive protien and creatinine were natural log transformed to approach approximate normality before regression analysis.

Suppl. Table 2. Characteristics of participants in the replication cohorts. Results are presented as mean (SD) for continuous traits and percentage for categorical traits.

Trait	FHS	EPIC-Norfolk
Sample Size	2,992	1,000
Age (yrs)	59.0 (9.7)	69.3 (7.3)
Female (%)	54	52
Current smoking (%)	15	18
Type 2 diabetes (%)	11	4
Body mass index (kg/m^2)	27.9 (5.1)	26.7 (4.0)
Diastolic blood pressure (mmHg)	75 (9)	85.5 (11.9)
Systolic blood pressure (mmHg)	128 (19)	143.7 (18.9)
Plasma L-arginine (µmol/L)	78.9 (27.9)	52.7 (16.6)

Footnotes: FHS, Framingham Heart Study; EPIC-Norfolk, the European Prospective Investigation into Cancer, Norfolk.

Suppl. Table 3. SNPs associated with serum L-arginine levels in combined analysis of European (N = 901) and Indian Asian (N = 1,394) samples ($p<5\times10^{-8}$).

SNP	Chromosome: Position	EA	AA	European			Indian Asian			Meta			
				EAF	Effect (SE)	P	EAF	Effect (SE)	P	Effect (SE)	P	P-het	Function Class
rs2292428	4:187121070	C	T	0.41	-3.3 (1.5)	3×10^{-2}	0.53	-6.9 (1.3)	9×10^{-8}	-5.4 (1.0)	5×10^{-8}	0.07	CYP4V2 intron
rs6835839	4:187123582	G	T	0.41	-3.3 (1.5)	3×10^{-2}	0.53	-6.9 (1.3)	8×10^{-8}	-5.4 (1.0)	5×10^{-8}	0.07	CYP4V2 intron
rs34733777	4:187126857	C	A	0.41	-3.2 (1.5)	4×10^{-2}	0.53	-7.5 (1.3)	6×10^{-9}	-5.7 (1.0)	8×10^{-9}	0.03	CYP4V2 intron
rs1473597	4:187127817	G	A	0.41	-3.2 (1.5)	4×10^{-2}	0.53	-7.4 (1.3)	7×10^{-9}	-5.7 (1.0)	8×10^{-9}	0.03	CYP4V2 intron
rs6552964	4:187128491	G	A	0.41	-3.2 (1.5)	3×10^{-2}	0.53	-7.5 (1.3)	6×10^{-9}	-5.7 (1.0)	7×10^{-9}	0.03	CYP4V2 intron
rs6552965	4:187128553	G	A	0.40	-2.8 (1.5)	7×10^{-2}	0.53	-7.5 (1.3)	6×10^{-9}	-5.6 (1.0)	2×10^{-8}	0.02	CYP4V2 intron
rs12508707	4:187128580	A	G	0.43	4.3 (1.6)	7×10^{-2}	0.31	8.0 (1.5)	8×10^{-8}	6.3 (1.1)	8×10^{-9}	0.09	CYP4V2 intron
rs9685463	4:187129771	A	G	0.41	-3.4 (1.5)	3×10^{-2}	0.53	-7.5 (1.3)	6×10^{-9}	-5.8 (1.0)	5×10^{-9}	0.04	CYP4V2 intron
rs7377304	4:187129780	G	T	0.49	5.3 (1.5)	4×10^{-4}	0.32	7.9 (1.4)	9×10^{-9}	6.7 (1.0)	4×10^{-11}	0.2	CYP4V2 intron
rs9684134	4:187129814	G	A	0.41	-3.3 (1.5)	3×10^{-2}	0.53	-7.4 (1.3)	7×10^{-9}	-5.7 (1.0)	6×10^{-9}	0.04	CYP4V2 intron
rs2276917	4:187129995	G	A	0.41	-3.3 (1.5)	3×10^{-2}	0.53	-7.4 (1.3)	7×10^{-9}	-5.7 (1.0)	7×10^{-9}	0.04	CYP4V2 intron
rs1053094	4:187133031	T	A	0.49	5.5 (1.6)	2×10^{-4}	0.33	7.9 (1.4)	1×10^{-8}	6.8 (1.0)	3×10^{-11}	0.25	CYP4V2 utr-3-prime
rs35834666	4:187138175	C	T	0.11	-6.4 (2.4)	7×10^{-3}	0.18	-8.3 (1.7)	1×10^{-6}	-7.6 (1.4)	4×10^{-8}	0.52	NA
rs13136536	4:187138463	G	C	0.63	6.2 (1.5)	4×10^{-5}	0.58	6.0 (1.3)	6×10^{-6}	6.1 (1.0)	1×10^{-9}	0.94	NA
rs12639909	4:187138801	A	G	0.11	9.1 (2.5)	2×10^{-4}	0.23	9.3 (1.5)	7×10^{-10}	9.3 (1.3)	7×10^{-13}	0.93	NA
rs34852777	4:187139062	C	T	0.11	-6.4 (2.4)	7×10^{-3}	0.18	-8.3 (1.7)	1×10^{-6}	-7.7 (1.4)	3×10^{-8}	0.52	NA
rs12331618	4:187139939	G	A	0.52	8.8 (1.5)	3×10^{-9}	0.40	10.8 (1.3)	2×10^{-16}	9.9 (1.0)	1×10^{-23}	0.3	NA
rs58370149	4:187143546	C	G	0.11	9.0 (2.5)	3×10^{-4}	0.24	9.0 (1.5)	2×10^{-9}	9.0 (1.3)	2×10^{-12}	0.99	NA
rs11132382	4:187143802	G	T	0.52	8.8 (1.5)	3×10^{-9}	0.40	10.6 (1.3)	5×10^{-16}	9.8 (1.0)	2×10^{-23}	0.36	NA
rs4862669	4:187145222	C	G	0.52	8.8 (1.5)	3×10^{-9}	0.40	10.5 (1.3)	6×10^{-16}	9.8 (1.0)	2×10^{-23}	0.37	NA
rs35669195	4:187146559	C	T	0.11	-6.5 (2.4)	6×10^{-3}	0.17	-8.2 (1.7)	1×10^{-6}	-7.6 (1.4)	4×10^{-8}	0.57	KLKB1 upstream-2KB
rs9994208	4:187146687	G	A	0.63	6.5 (1.5)	2×10^{-5}	0.58	5.8 (1.3)	8×10^{-6}	6.1 (1.0)	6×10^{-10}	0.75	KLKB1 upstream-2KB
rs4253236	4:187148071	C	T	0.63	6.4 (1.5)	2×10^{-5}	0.57	5.9 (1.3)	7×10^{-6}	6.1 (1.0)	6×10^{-10}	0.77	KLKB1 upstream-2KB
rs2048	4:187148133	T	G	0.52	8.8 (1.5)	3×10^{-9}	0.40	10.5 (1.3)	7×10^{-16}	9.7 (1.0)	2×10^{-23}	0.38	KLKB1 upstream-2KB
rs4253238	4:187148387	T	C	0.52	8.8 (1.5)	3×10^{-9}	0.40	10.5 (1.3)	7×10^{-16}	9.7 (1.0)	2×10^{-23}	0.38	KLKB1 upstream-2KB

SNP	Chromosome: Position	EA	AA	European			Indian Asian			Meta			
				EAF	Effect (SE)	P	EAF	Effect (SE)	P	Effect (SE)	P	P-het	Function Class
rs1912826	4:187149540	A	G	0.52	8.7 (1.5)	2×10^{-9}	0.40	10.5 (1.3)	6×10^{-16}	9.8 (1.0)	3×10^{-23}	0.36	KLKB1 intron
rs3775298	4:187150478	G	A	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.5 (1.3)	9×10^{-16}	9.8 (1.0)	2×10^{-23}	0.4	KLKB1 intron
rs1511801	4:187150710	T	A	0.52	8.9 (1.5)	1×10^{-9}	0.40	10.5 (1.3)	9×10^{-16}	9.8 (1.0)	1×10^{-23}	0.44	KLKB1 intron
rs4241815	4:187152142	T	C	0.52	8.9 (1.5)	2×10^{-9}	0.40	10.6 (1.3)	6×10^{-16}	9.8 (1.0)	1×10^{-23}	0.39	KLKB1 intron
rs4241816	4:187152327	T	A	0.52	8.9 (1.5)	2×10^{-9}	0.40	10.6 (1.3)	6×10^{-16}	9.8 (1.0)	1×10^{-23}	0.38	KLKB1 intron
rs4241817	4:187152658	C	T	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.6 (1.3)	6×10^{-16}	9.8 (1.0)	1×10^{-23}	0.38	KLKB1 intron
rs4253244	4:187153775	A	C	0.63	6.5 (1.5)	2×10^{-5}	0.58	5.9 (1.3)	6×10^{-16}	6.2 (1.0)	5×10^{-10}	0.79	KLKB1 intron
rs4241818	4:187153786	C	T	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.6 (1.3)	6×10^{-16}	9.8 (1.0)	1×10^{-23}	0.37	KLKB1 intron
rs4253248	4:187155488	A	G	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.7 (1.3)	3×10^{-16}	9.9 (1.0)	7×10^{-24}	0.34	KLKB1 intron
rs4241819	4:187157140	T	C	0.48	8.2 (1.5)	7×10^{-8}	0.35	10.8 (1.4)	2×10^{-14}	9.6 (1.0)	2×10^{-20}	0.21	KLKB1 intron
rs4861708	4:187157233	A	G	0.38	6.6 (1.7)	6×10^{-5}	0.28	11.3 (1.6)	4×10^{-12}	9.0 (1.2)	9×10^{-15}	0.05	KLKB1 intron
rs4253252	4:187157458	G	T	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.7 (1.3)	4×10^{-16}	9.9 (1.0)	9×10^{-24}	0.35	KLKB1 intron
rs3733402	4:187158034	A	G	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.7 (1.3)	4×10^{-16}	9.9 (1.0)	1×10^{-23}	0.34	KLKB1 missense
rs4253254	4:187158508	T	C	0.52	8.8 (1.5)	3×10^{-9}	0.40	10.7 (1.3)	4×10^{-16}	9.8 (1.0)	1×10^{-23}	0.32	KLKB1 intron
rs4253255	4:187158922	C	G	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.7 (1.3)	3×10^{-16}	9.9 (1.0)	8×10^{-24}	0.34	KLKB1 intron
rs4253256	4:187159282	C	G	0.63	6.4 (1.5)	2×10^{-5}	0.58	6.0 (1.3)	4×10^{-6}	6.2 (1.0)	4×10^{-10}	0.83	KLKB1 intron
rs4241820	4:187160081	T	C	0.63	6.2 (1.6)	2×10^{-4}	0.45	8.7 (1.3)	8×10^{-11}	7.7 (1.0)	1×10^{-13}	0.24	KLKB1 intron
rs12509937	4:187160250	T	C	0.41	8.6 (1.6)	9×10^{-8}	0.33	10.6 (1.5)	6×10^{-13}	9.7 (1.1)	5×10^{-19}	0.36	KLKB1 intron
rs139276089	4:187160394	C	G	0.34	6.3 (1.7)	3×10^{-4}	0.23	9.6 (1.8)	7×10^{-8}	7.9 (1.3)	3×10^{-10}	0.18	KLKB1 intron
rs71640034	4:187161048	A	G	0.46	8.1 (1.5)	1×10^{-7}	0.37	10.9 (1.4)	1×10^{-15}	9.7 (1.0)	2×10^{-21}	0.18	KLKB1 intron
rs71640036	4:187161120	T	G	0.50	9.1 (1.5)	1×10^{-9}	0.39	11.2 (1.3)	5×10^{-17}	10.3 (1.0)	1×10^{-24}	0.31	KLKB1 intron
rs66530140	4:187161211	C	T	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.8 (1.3)	2×10^{-16}	9.9 (1.0)	7×10^{-24}	0.32	KLKB1 intron
rs35984397	4:187161501	A	G	0.52	8.8 (1.5)	2×10^{-9}	0.40	10.8 (1.3)	2×10^{-16}	9.9 (1.0)	7×10^{-24}	0.32	KLKB1 intron
rs4253266	4:187163369	T	C	0.26	-6.3 (1.7)	2×10^{-4}	0.24	-7.9 (1.6)	6×10^{-7}	-7.2 (1.2)	7×10^{-10}	0.51	KLKB1 intron
rs4253269	4:187163511	T	C	0.30	-6.2 (1.6)	1×10^{-4}	0.28	-7.4 (1.5)	4×10^{-7}	-6.8 (1.1)	3×10^{-10}	0.57	KLKB1 intron
rs4253271	4:187163612	T	G	0.48	8.3 (1.5)	5×10^{-8}	0.37	10.9 (1.4)	2×10^{-15}	9.7 (1.0)	2×10^{-21}	0.2	KLKB1 intron
rs4253272	4:187163614	T	C	0.48	8.1 (1.5)	9×10^{-8}	0.38	10.9 (1.4)	2×10^{-15}	9.6 (1.0)	3×10^{-21}	0.17	KLKB1 intron
rs4253273	4:187163626	G	C	0.67	5.9 (1.6)	3×10^{-4}	0.47	8.3 (1.3)	1×10^{-10}	7.4 (1.0)	4×10^{-13}	0.24	KLKB1 intron

SNP	Chromosome: Position	EA	AA	European			Indian Asian			Meta			
				EAF	Effect (SE)	P	EAF	Effect (SE)	P	Effect (SE)	P	P-het	Function Class
rs61000956	4:187164081	C	T	0.34	8.5 (1.7)	7×10^{-7}	0.33	11.2 (1.5)	9×10^{-15}	10.1 (1.1)	9×10^{-20}	0.21	KLKB1 intron
rs4253281	4:187164349	A	G	0.51	8.6 (1.5)	7×10^{-9}	0.40	10.7 (1.3)	5×10^{-16}	9.7 (1.0)	5×10^{-23}	0.29	KLKB1 intron
rs4253282	4:187164399	T	C	0.53	8.8 (1.5)	3×10^{-9}	0.40	10.7 (1.3)	3×10^{-16}	9.9 (1.0)	9×10^{-24}	0.34	KLKB1 intron
rs4253283	4:187165211	C	T	0.69	7.7 (1.6)	2×10^{-6}	0.47	8.0 (1.3)	5×10^{-10}	7.9 (1.0)	6×10^{-15}	0.9	KLKB1 intron
rs34899763	4:187165433	A	T	0.70	7.6 (1.6)	3×10^{-6}	0.48	8.7 (1.3)	1×10^{-11}	8.3 (1.0)	2×10^{-16}	0.61	KLKB1 intron
rs144276707	4:187165700	A	G	0.11	9.0 (2.5)	2×10^{-3}	0.23	9.0 (1.5)	4×10^{-9}	9.0 (1.3)	5×10^{-12}	0.98	KLKB1 intron
rs4253289	4:187167103	C	A	0.11	9.1 (2.5)	2×10^{-3}	0.23	9.2 (1.5)	1×10^{-9}	9.2 (1.3)	1×10^{-12}	0.96	KLKB1 intron
rs13134749	4:187167682	T	C	0.12	-7.3 (2.3)	2×10^{-3}	0.19	-7.5 (1.7)	7×10^{-6}	-7.4 (1.4)	4×10^{-8}	0.95	KLKB1 intron
rs1973612	4:187169167	T	C	0.51	8.9 (1.5)	4×10^{-9}	0.39	10.9 (1.3)	2×10^{-16}	10.0 (1.0)	1×10^{-23}	0.32	KLKB1 intron
rs149893292	4:187169359	A	G	0.14	9.5 (2.2)	1×10^{-5}	0.25	9.2 (1.5)	8×10^{-10}	9.3 (1.2)	5×10^{-14}	0.9	KLKB1 intron
rs2203111	4:187169469	A	G	0.12	-6.8 (2.3)	3×10^{-3}	0.19	-7.6 (1.7)	3×10^{-6}	-7.4 (1.3)	4×10^{-8}	0.77	KLKB1 intron
rs4253294	4:187169650	G	A	0.70	7.7 (1.6)	2×10^{-6}	0.48	8.7 (1.3)	7×10^{-12}	8.3 (1.0)	1×10^{-16}	0.62	KLKB1 intron
rs4253306	4:187174030	T	G	0.11	9.0 (2.5)	2×10^{-4}	0.23	9.0 (1.5)	2×10^{-9}	9.0 (1.3)	2×10^{-12}	0.99	KLKB1 intron
rs4253311	4:187174683	G	A	0.52	8.8 (1.5)	2×10^{-9}	0.39	10.5 (1.3)	6×10^{-16}	9.8 (1.0)	1×10^{-23}	0.39	KLKB1 intron
rs4253313	4:187175177	G	A	0.70	7.8 (1.6)	2×10^{-6}	0.47	8.2 (1.4)	8×10^{-11}	8.0 (1.0)	7×10^{-16}	0.84	KLKB1 intron
rs4253315	4:187175457	T	C	0.11	9.0 (2.5)	3×10^{-4}	0.22	9.1 (1.5)	2×10^{-9}	9.0 (1.3)	3×10^{-12}	0.99	KLKB1 intron
rs3775302	4:187177814	G	A	0.14	9.3 (2.2)	2×10^{-5}	0.23	9.1 (1.5)	1×10^{-9}	9.2 (1.2)	1×10^{-13}	0.92	KLKB1 intron
rs4861709	4:187178186	T	C	0.70	7.9 (1.6)	2×10^{-6}	0.48	8.6 (1.3)	1×10^{-11}	8.3 (1.0)	1×10^{-16}	0.75	KLKB1 intron
rs4253325	4:187178473	A	G	0.11	8.8 (2.5)	3×10^{-4}	0.23	9.0 (1.5)	2×10^{-9}	9.0 (1.3)	3×10^{-12}	0.95	KLKB1 missense
rs28671360	4:187178788	G	A	0.71	7.9 (1.6)	2×10^{-6}	0.48	8.6 (1.3)	9×10^{-12}	8.3 (1.0)	9×10^{-17}	0.72	KLKB1 intron
rs925453	4:187179210	C	T	0.71	7.9 (1.6)	2×10^{-6}	0.48	8.7 (1.3)	6×10^{-12}	8.4 (1.0)	6×10^{-17}	0.70	KLKB1 synonymous-codon
rs4253332	4:187179803	C	T	0.70	7.8 (1.7)	2×10^{-6}	0.48	8.7 (1.3)	8×10^{-12}	8.4 (1.0)	1×10^{-16}	0.68	KLKB1 downstream-500B
rs12186258	4:187183502	A	G	0.55	5.1 (1.6)	1×10^{-3}	0.36	7.0 (1.4)	1×10^{-6}	6.2 (1.1)	1×10^{-8}	0.38	NA
rs4253416	4:187197994	T	C	0.56	5.9 (1.6)	2×10^{-4}	0.54	5.7 (1.3)	2×10^{-5}	5.8 (1.0)	2×10^{-8}	0.92	F11 intron
rs1801020	5:176836532	G	A	0.76	7.8 (1.8)	1×10^{-5}	0.57	6.8 (1.3)	2×10^{-7}	7.1 (1.1)	1×10^{-11}	0.63	F12 utr-variant-5-prime
rs2731674	5:176839890	G	T	0.76	7.8 (1.8)	1×10^{-5}	0.56	6.7 (1.3)	2×10^{-7}	7.1 (1.0)	1×10^{-11}	0.62	NA
rs2731673	5:176839898	C	T	0.76	7.9 (1.8)	1×10^{-5}	0.57	6.7 (1.3)	2×10^{-7}	7.0 (1.0)	2×10^{-11}	0.61	NA
rs2545801	5:176841339	C	T	0.76	7.9 (1.8)	9×10^{-6}	0.56	6.8 (1.3)	1×10^{-7}	7.1 (1.0)	7×10^{-12}	0.60	NA

SNP	Chromosome: Position	EA	AA	European			Indian Asian			Meta			
				EAF	Effect (SE)	P	EAF	Effect (SE)	P	Effect (SE)	P	P-het	Function Class
rs2731672	5:176842474	C	T	0.76	7.6 (1.7)	2×10^{-5}	0.56	6.3 (1.3)	5×10^{-7}	6.7 (1.0)	3×10^{-11}	0.53	NA

Footnote: EA, effect allele; AA, alternate allele; EAF, effect allele frequency; Effect, effect size per copy of the effect allele; SE, standard error; P-het, P value for the heterogeneity test between the two ethnic groups. Lambdas are 1.008 for European, 1.004 for Indian Asian, and 1.002 for combined analysis.

Suppl. Table 4. SNPs with suggestive associations with serum L-arginine levels in combined analysis of European and Indian Asian samples (N = 2,295, $5\times10^{-8} < p < 1\times10^{-5}$).

SNP	Chromosome:Position	EA	AA	EAF	Effect	SE	P	P-het	Gene and function class
rs1036588	2:5599612	A	C	0.81	-6.0	1.2	1×10^{-6}	0.98	NA
rs77488517	2:5600476	T	C	0.19	6.2	1.2	5×10^{-7}	0.86	NA
rs78969375	2:5600563	A	T	0.81	-6.2	1.2	5×10^{-7}	0.86	NA
rs17293732	2:5602284	T	C	0.81	-6.0	1.2	9×10^{-7}	0.77	NA
rs700960	2:5603666	A	G	0.23	5.4	1.2	3×10^{-6}	0.47	NA
rs57543999	2:5604048	T	C	0.20	6.0	1.2	8×10^{-7}	0.77	NA
rs792094	2:5604166	C	G	0.20	6.0	1.2	8×10^{-7}	0.77	NA
rs60196128	2:5604584	A	G	0.20	6.0	1.2	8×10^{-7}	0.78	NA
rs59212612	2:5604637	T	C	0.80	-6.0	1.2	8×10^{-7}	0.78	NA
rs10180670	2:5607349	A	G	0.20	5.8	1.2	1×10^{-6}	0.68	NA
rs16863805	2:5610906	A	G	0.20	5.8	1.2	1×10^{-6}	0.68	NA
rs6743805	2:5612810	A	T	0.20	5.5	1.2	3×10^{-6}	0.60	NA
rs60572809	2:5613376	A	C	0.20	5.5	1.2	3×10^{-6}	0.59	NA
rs76549602	2:5613910	T	C	0.80	-5.5	1.2	3×10^{-6}	0.57	NA
rs17360123	2:5614214	T	G	0.20	5.5	1.2	3×10^{-6}	0.58	NA
rs56277937	2:5614459	T	C	0.20	5.8	1.2	1×10^{-6}	0.60	NA
rs77737322	3:171891992	A	G	0.96	-16.5	3.4	1×10^{-6}	0.15	FNDC3B intron
rs2292429	4:187121126	A	T	0.44	-5.4	1.0	1×10^{-7}	0.07	CYP4V2 intron
rs2292430	4:187121127	A	T	0.56	5.4	1.0	2×10^{-7}	0.09	CYP4V2 intron
rs3736456	4:187122355	T	C	0.86	-6.8	1.5	9×10^{-6}	0.89	CYP4V2 synonymous-codon
rs7661584	4:187125102	C	G	0.14	7.3	1.5	5×10^{-7}	0.80	CYP4V2 intron
rs6552963	4:187128478	A	G	0.53	5.0	1.0	5×10^{-7}	0.08	CYP4V2 intron
rs4862664	4:187136127	T	C	0.86	-7.3	1.5	9×10^{-7}	0.60	NA
rs10004932	4:187137482	A	G	0.57	-4.7	1.0	3×10^{-6}	0.10	NA
rs28797242	4:187140276	T	C	0.29	5.3	1.1	3×10^{-6}	0.49	NA
rs74508932	4:187141704	A	C	0.84	6.4	1.4	7×10^{-6}	0.38	NA

SNP	Chromosome:Position	EA	AA	EAF	Effect	SE	P	P-het	Gene and function class
rs2221843	4:187144200	C	G	0.72	5.3	1.1	2×10^{-6}	0.63	NA
rs13102931	4:187145626	T	G	0.15	-7.5	1.4	6×10^{-8}	0.60	NA
rs13102788	4:187145738	T	C	0.15	-7.5	1.4	6×10^{-8}	0.60	NA
rs10014399	4:187146359	C	G	0.72	5.3	1.1	2×10^{-6}	0.61	NA
rs4253241	4:187149233	T	C	0.85	7.5	1.4	5×10^{-8}	0.63	KLKB1 intron
rs1511802	4:187150806	T	C	0.71	-5.3	1.1	3×10^{-6}	0.50	KLKB1 intron
rs4253243	4:187153511	T	C	0.84	6.3	1.4	8×10^{-6}	0.37	KLKB1 intron
rs4253246	4:187154424	A	T	0.84	7.5	1.4	5×10^{-8}	0.68	KLKB1 intron
rs4253251	4:187156473	C	G	0.28	-5.3	1.1	2×10^{-6}	0.69	KLKB1 intron
rs184644242	4:187157181	T	G	0.84	7.4	1.4	6×10^{-8}	0.60	KLKB1 intron
rs145549717	4:187157232	T	C	0.18	-6.3	1.4	3×10^{-6}	0.78	KLKB1 intron
rs4253253	4:187158433	A	G	0.72	-5.8	1.2	1×10^{-6}	0.65	KLKB1 intron
rs71640035	4:187161061	T	G	0.74	-5.7	1.2	4×10^{-6}	0.60	KLKB1 intron
rs114652910	4:187161317	T	G	0.84	7.4	1.4	8×10^{-8}	0.73	KLKB1 intron
rs28380417	4:187161506	A	T	0.28	-5.4	1.1	1×10^{-6}	0.66	KLKB1 intron
rs4253259	4:187162048	T	G	0.08	9.9	2.0	5×10^{-7}	0.48	KLKB1 intron
rs13126698	4:187163268	T	C	0.84	7.3	1.4	1×10^{-7}	0.76	KLKB1 intron
rs4253274	4:187163652	T	G	0.28	-5.3	1.1	2×10^{-6}	0.65	KLKB1 intron
rs4253276	4:187163859	C	G	0.12	7.6	1.7	5×10^{-6}	0.57	KLKB1 intron
rs4253277	4:187163881	A	G	0.72	5.3	1.1	2×10^{-6}	0.68	KLKB1 intron
rs4253284	4:187165526	A	G	0.84	7.2	1.4	1×10^{-7}	0.79	KLKB1 intron
rs80177406	4:187166024	A	G	0.28	5.6	1.2	2×10^{-6}	0.49	KLKB1 intron
rs35792324	4:187167882	C	G	0.16	-7.4	1.4	8×10^{-8}	0.79	KLKB1 intron
rs4253290	4:187168438	T	C	0.16	-7.3	1.4	9×10^{-8}	0.79	KLKB1 intron
rs2175494	4:187168782	A	T	0.72	5.3	1.1	2×10^{-6}	0.70	KLKB1 intron
rs2175495	4:187169123	T	C	0.29	5.5	1.1	1×10^{-6}	0.43	KLKB1 intron
rs2137145	4:187169266	A	G	0.28	-5.3	1.1	2×10^{-6}	0.68	KLKB1 intron
rs4253295	4:187170222	A	G	0.71	-5.5	1.1	1×10^{-6}	0.43	KLKB1 intron
rs4253296	4:187170545	T	C	0.84	7.2	1.4	1×10^{-7}	0.83	KLKB1 intron

SNP	Chromosome:Position	EA	AA	EAF	Effect	SE	P	P-het	Gene and function class
rs4253297	4:187170747	T	C	0.29	5.5	1.1	1×10^{-6}	0.45	KLKB1 intron
rs4253299	4:187171355	A	G	0.28	-5.3	1.1	2×10^{-6}	0.70	KLKB1 intron
rs2304595	4:187172280	A	G	0.30	6.1	1.1	5×10^{-8}	0.73	KLKB1 intron
rs4253301	4:187173012	T	G	0.84	7.0	1.3	2×10^{-7}	0.89	KLKB1 missense
rs4253303	4:187173546	A	G	0.29	5.5	1.1	1×10^{-6}	0.45	KLKB1 intron
rs4253304	4:187173571	C	G	0.30	6.1	1.1	7×10^{-8}	0.71	KLKB1 intron
rs4253305	4:187173691	A	G	0.70	-6.1	1.1	7×10^{-8}	0.71	KLKB1 intron
rs4253308	4:187174363	A	C	0.71	-5.5	1.1	1×10^{-6}	0.45	KLKB1 intron
rs4253314	4:187175235	T	C	0.16	-7.1	1.3	1×10^{-7}	0.90	KLKB1 intron
rs2292423	4:187175722	A	T	0.30	6.1	1.1	6×10^{-8}	0.73	KLKB1 intron
rs4253320	4:187176626	T	C	0.29	5.5	1.1	1×10^{-6}	0.48	KLKB1 intron
rs4241821	4:187176834	T	C	0.28	-5.3	1.1	2×10^{-6}	0.70	KLKB1 intron
rs3775303	4:187178014	A	T	0.70	-6.1	1.1	5×10^{-8}	0.76	KLKB1 intron
rs4241822	4:187178300	T	C	0.70	-5.7	1.1	3×10^{-7}	0.78	KLKB1 intron
rs4253326	4:187178599	T	C	0.72	5.3	1.1	2×10^{-6}	0.71	KLKB1 intron
rs4253331	4:187179135	T	C	0.84	6.3	1.4	8×10^{-6}	0.33	KLKB1 intron
rs3822055	4:187179678	T	C	0.28	-5.2	1.1	3×10^{-6}	0.79	KLKB1 downstream-500B
rs13151625	4:187180655	A	G	0.84	7.4	1.4	8×10^{-8}	0.90	NA
rs58527029	4:187182093	A	G	0.89	-7.6	1.7	6×10^{-6}	0.52	NA
rs59634726	4:187182296	A	C	0.11	7.6	1.7	7×10^{-6}	0.51	NA
rs2055916	4:187196510	A	G	0.48	4.5	1.0	9×10^{-6}	0.75	F11 intron
rs4253415	4:187197943	A	T	0.83	6.8	1.4	6×10^{-7}	0.90	F11 intron
rs36054182	4:187212987	A	G	0.17	-6.4	1.3	2×10^{-6}	0.84	F11-AS1 intron
rs13145616	4:187215016	A	C	0.19	-5.7	1.3	7×10^{-6}	0.28	F11-AS1 intron
rs4976691	5:176827815	C	G	0.45	-5.1	1.1	1×10^{-6}	0.98	PFN3 upstream-2KB
rs17876032	5:176830627	A	G	0.55	5.2	1.1	1×10^{-6}	0.88	F12 intron
rs17876031	5:176831119	A	G	0.44	-5.2	1.1	1×10^{-6}	0.89	F12 intron
rs4976649	5:176833415	A	G	0.47	5.0	1.1	7×10^{-6}	0.93	F12 intron
rs140783283	6:31306779	A	G	0.53	4.4	1.0	8×10^{-6}	0.46	NA

SNP	Chromosome:Position	EA	AA	EAF	Effect	SE	P	P-het	Gene and function class
rs2781668	6:131897278	T	C	0.20	5.8	1.2	2×10^{-6}	0.03	ARG1 intron
rs2246012	6:131898208	T	C	0.78	-5.8	1.2	7×10^{-7}	0.02	ARG1 intron
rs2608985	6:131917379	A	G	0.78	-5.8	1.2	5×10^{-7}	0.01	MED23 intron
rs2608984	6:131918839	A	T	0.78	-5.8	1.2	5×10^{-7}	0.01	MED23 intron
rs2248551	6:131924689	A	G	0.22	5.8	1.2	5×10^{-7}	0.01	MED23 intron
rs2608953	6:131926334	T	C	0.22	5.7	1.2	9×10^{-7}	0.01	MED23 intron
rs2245133	6:131931092	T	C	0.78	-5.8	1.2	7×10^{-6}	0.02	MED23 intron
rs3756785	6:131950401	T	C	0.78	-5.7	1.2	1×10^{-6}	0.01	MED23 upstream-2KB
rs3843995	6:131950798	A	G	0.78	-5.7	1.2	1×10^{-6}	0.01	MED23 upstream-2KB
rs73550998	6:131960039	T	C	0.77	-5.3	1.2	6×10^{-6}	0.02	ENPP3 intron
rs12663047	6:131960898	A	G	0.78	-5.2	1.2	8×10^{-6}	0.02	ENPP3 intron
rs3850246	6:131965872	T	G	0.22	5.2	1.2	8×10^{-6}	0.02	ENPP3 intron
rs140018894	7:64388840	A	G	0.98	-28.8	5.8	6×10^{-7}	0.58	ZNF273 synonymous-codon / nc-transcript
rs113262228	8:70458044	T	G	0.02	20.5	4.1	4×10^{-7}	0.60	SULF1 intron
rs12342073	9:107063809	T	C	0.10	8.4	1.8	5×10^{-6}	0.72	NA
rs75256538	11:11049373	T	C	0.10	7.8	1.7	6×10^{-6}	0.49	NA
rs59772322	11:11052230	C	G	0.90	-7.8	1.6	2×10^{-6}	0.46	NA
rs60940583	11:11052364	T	C	0.10	7.6	1.7	8×10^{-6}	0.53	NA
rs74986670	11:11054362	A	C	0.10	7.6	1.7	8×10^{-6}	0.55	NA
rs7928883	11:11054491	T	C	0.10	7.6	1.7	8×10^{-6}	0.55	NA
rs77775723	11:16377045	A	G	0.11	-7.5	1.6	5×10^{-6}	0.52	SOX6 intron
rs12805751	11:16379906	T	C	0.89	7.5	1.6	5×10^{-6}	0.52	SOX6 intron
rs76908888	11:16381377	A	G	0.11	-7.5	1.6	5×10^{-6}	0.53	SOX6 intron
rs34617734	11:16381919	A	C	0.11	-7.6	1.7	5×10^{-6}	0.53	SOX6 intron
rs10769478	11:48838364	T	G	0.28	7.0	1.6	8×10^{-6}	0.04	NA
rs2192139	12:11012676	A	C	0.17	-5.9	1.3	7×10^{-6}	0.74	PRH1-PRR4 intron
rs10845223	12:11013739	T	G	0.83	5.9	1.3	7×10^{-6}	0.73	PRH1-PRR4 intron
rs7978300	12:11013926	T	C	0.15	-6.1	1.4	1×10^{-5}	0.61	PRH1-PRR4 intron

SNP	Chromosome:Position	EA	AA	EAF	Effect	SE	P	P-het	Gene and function class
rs965243	12:11021008	A	T	0.83	5.8	1.3	1×10^{-5}	0.72	PRH1-PRR4 intron
rs112458672	12:53257605	A	G	0.08	-8.4	1.8	6×10^{-6}	0.64	NA
rs1405462	12:131491589	A	G	0.33	-5.2	1.2	7×10^{-6}	0.25	GPR133 intron
rs191118886	14:23202906	A	G	0.02	23.8	4.6	2×10^{-7}	0.27	NA
rs12890532	14:91087638	T	C	0.71	-5.7	1.3	9×10^{-6}	0.43	TTC7B intron
rs11074732	16:25924212	A	G	0.70	5.3	1.2	6×10^{-6}	0.97	HS3ST4 intron
rs4787785	16:25925254	A	G	0.30	-5.3	1.2	7×10^{-6}	0.92	HS3ST4 intron
rs62639554	16:25925744	T	G	0.30	-5.3	1.2	5×10^{-6}	0.99	HS3ST4 intron
rs2526062	16:74047671	A	C	0.27	-5.3	1.1	2×10^{-6}	0.49	NA
rs147395646	18:65272325	C	G	0.94	-10.8	2.4	5×10^{-6}	0.44	LOC643542 intron
rs117063294	18:65278962	A	G	0.06	10.6	2.3	5×10^{-6}	0.46	LOC643542 intron
rs7258587	19:37985806	C	G	0.04	17.5	3.8	4×10^{-6}	0.87	NA
rs6126720	20:51629366	A	C	0.06	-8.9	2.0	1×10^{-6}	0.42	TSHZ2 intron
rs16997425	20:51629429	A	C	0.94	8.9	2.0	9×10^{-6}	0.29	TSHZ2 intron
rs6022211	20:51629630	A	G	0.06	-8.9	2.0	9×10^{-6}	0.29	TSHZ2 intron
rs6013600	20:51630425	T	C	0.06	-9.1	2.0	6×10^{-6}	0.33	TSHZ2 intron
rs6013601	20:51630780	T	C	0.06	-9.1	2.0	7×10^{-6}	0.25	TSHZ2 intron

Footnote: EA, effect allele; AA, alternate allele; EAF, effect allele frequency; Effect, effect size per copy of the effect allele; SE, standard error; P-het, P value for the heterogeneity test between the two ethnic groups. Lambdas are 1.008 for European, 1.004 for Indian Asian, and 1.002 for combined analysis.

Suppl. Table 5. eQTL analysis of the sentinel or its proxy SNPs.

SNP	EA/AA	Locus	Sample set	N	Effect	P	Pcorr†
Blood							
rs71640036	G/T	*KLKB1*	LOLIPOP	816	-0.004	5×10^{-1}	n.s.
		CYP4V2	LOLIPOP	816	-0.064	1×10^{-3}	1×10^{-2}
rs2545801	T/C	*F12*	LOLIPOP	816	-0.04	1×10^{-3}	4×10^{-2}
Liver							
rs71640036	G/T	*KLKB1*	NA	NA	NA	NA	NA
rs2731672*	T/C	*F12*	HLC	427	NA	1×10^{-23}	NA
			UC	206	-0.56	$<1 \times 10^{-16}$	NA
			UW	60	-0.37	2×10^{-6}	NA
			Merck	266	-0.18	2×10^{-13}	NA
			RYGB	651	NA	6×10^{-53}	NA

Footnote: EA, effect allele; AA, alternate allele; Effect, eQTL effect size per effect allele copy; N, eQTL study sample size; Blood, peripheral blood leucocytes. *proxy SNP for rs2545801 (r^2 = 0.99); †Pcorr, P value after bonferroni correction for 14 and 38 genes tested within 1Mb either side of the two sentinel SNPs rs71640036 and rs2545801, respectively, in blood samples. Listed are all genes with p-values < 0.05; n.s., non-significant; UC(1), University of Chicago; UW (1), university of Washington; Merk (1), Merk study; HLC (2), human liver cohort; RYGB (3), Roux-en-Y gastric bypass cohort in extreme obese patients; LOLIPOP, the LOLIPOP study; NA, data not available or non-applicable.

Suppl. Table 6. Association of sentinel SNPs (or their best available proxy) with other traits in published genome-wide association studies.

SNP	EA/AA	r^2	Trait	N	Effect	P
KLKB1						
rs3733402*	G/A	0.96	Histidine (4)	8,330	-0.11	6×10^{-11}
			Histidine / Valine (4)	8,330	-0.11	3×10^{-12}
			Alanine / Histidine (4)	8,330	0.11	3×10^{-12}
			Phenylalanine / Valine (4)	8,330	-0.10	1×10^{-10}
			Leucylphenylalanine (5)	1,260	-0.28	7×10^{-25}
			HXGXA (5)	1,260	-0.44	9×10^{-27}
			IGF-1 free (6)	815	0.04	9×10^{-8}
			Log plasma BNP (7)	2,790	0.20	2×10^{-11}
			Active plasma renin (8)	1,180	-0.06	7×10^{-5}
rs4253252*	T/G	0.96	des-arg(9) Bradykinin (9)	2,231	-0.24	7×10^{-18}
			hsCRP (10)	66,185	0.012	6×10^{-2}
rs1912826*	G/A	0.96	Phenylalanine (11)	6,608	< 0	4×10^{-12}
rs4253238*	C/T	0.96	MR-pro-ADM (12)	3,444	0.03	4×10^{-52}
			CT-pro-ET-1 (12)	3,444	5.14	1×10^{-122}
rs4253311*	A/G	0.96	Plasma renin activity (13)	5,275	-0.10	6×10^{-8}
F12						
rs2545801	T/C	-	aPTT (14)	11,851	1.68	7×10^{-88}
			Phenylalanine (4)	8,330	-0.12	9×10^{-11}
			des-arg(9) Bradykinin (15)	5,194	-0.16	1×10^{-17}
			Arginine / des-arg(9) Bradykinin (15)	6,054	-0.15	4×10^{-13}
			FXII antigen (16)	2100	-0.85	2×10^{-94}
rs2731672*	T/C	0.99	MR-pro-ADM (12)	3,444	0.02	6×10^{-24}
			CT-pro-ET-1 (12)	3,444	4.61	1×10^{-67}
rs1808020*	A/G	0.99	hsCRP (10)	66,185	-0.02	3×10^{-2}
			Active plasma renin (8)	1,179	-0.06	3×10^{-4}

Footnote: EA, effect allele (minor allele, all associated with reduced serum L-arginine levels); AA, alternate allele; r^2, LD with sentinel SNP (rs71640036 in *KLKB1* and rs2545801 in *F12* loci) in samples of European descent from this study; IGF-1, fasting serum insulin-like growth factor-1; BNP, B-Type Natriuretic Peptide; hsCRP, high-sensitivity C-reactive protein; MR-pro-ADM, plasma midregional-proadrenomedullin; CT-pro-ET-1, plasma C-terminal-pro-endothelin-1;

aPTT, activated partial thromboplastin time; NA, data not available; *proxy of its related sentinel SNP.

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