The American Journal of Human Genetics

Supplemental Data

Dominance Genetic Variation Contributes Little to the Missing Heritability for Human Complex Traits

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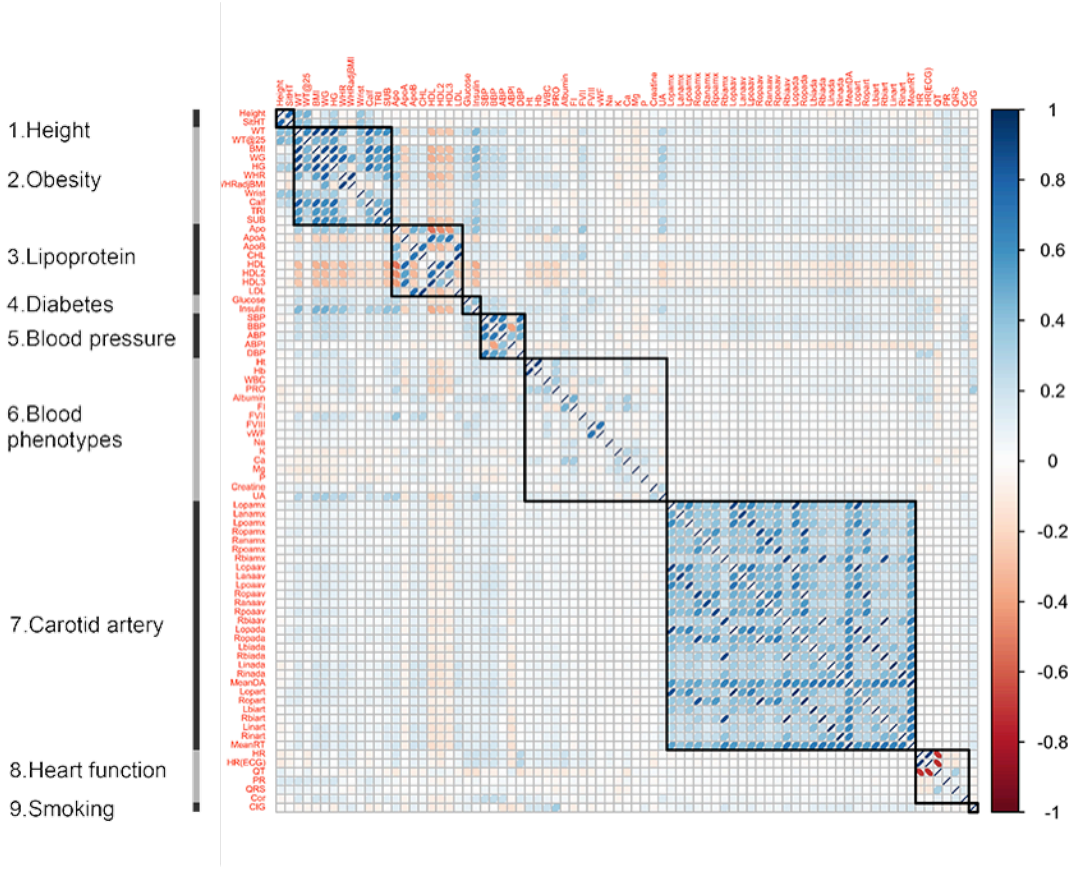

Figure S1. Pairwise phenotypic correlations between 79 quantitative traits in the ARIC cohort.

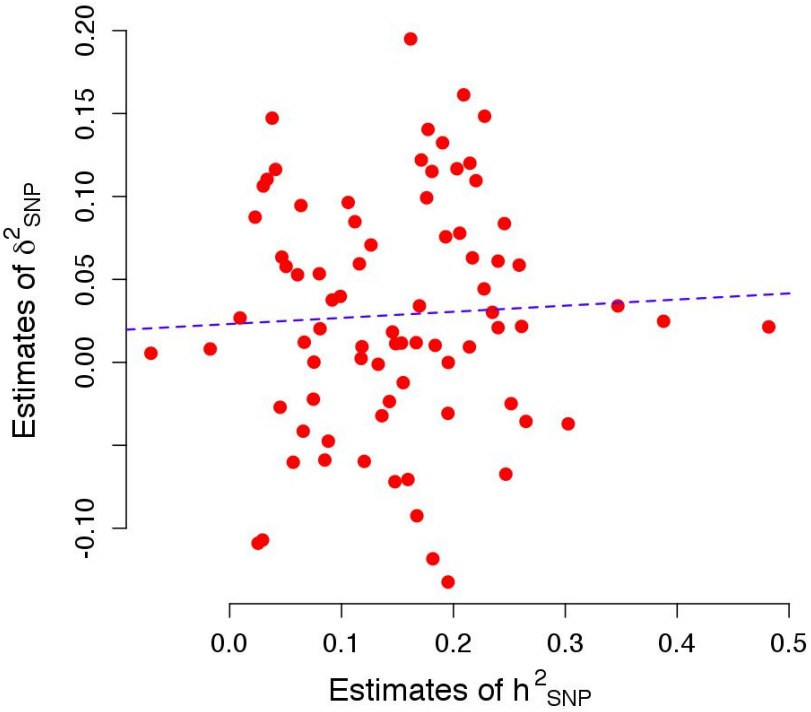

Figure S2. Estimate of δ^2_{SNP} against that of h^2_{SNP} in the ARIC cohort. The regression slope is 0.04, which is not significantly different from zero (P = 0.67).

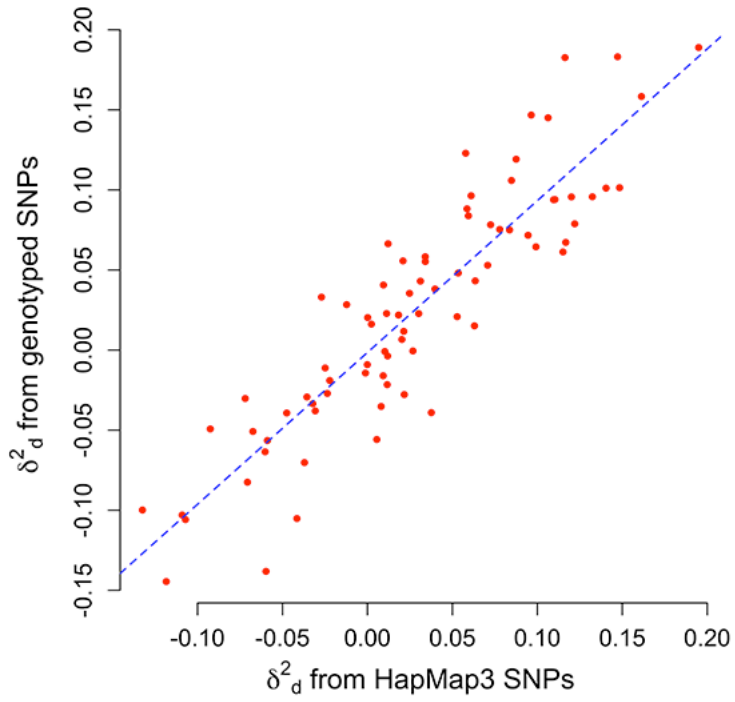

Figure S3. Plot of the estimates of δ^2_{SNP} using genotyped data against those using imputed data for the 79 traits in the ARIC cohort. The mean estimate of δ^2_{SNP} across all the 79 traits is 3% using genotype data, which is exactly the same as that using imputed data (HapMap phase 3 SNPs extracted from 1000G imputed data). The regression slope is 0.95 (SE=0.05), which is not significantly different from 1.

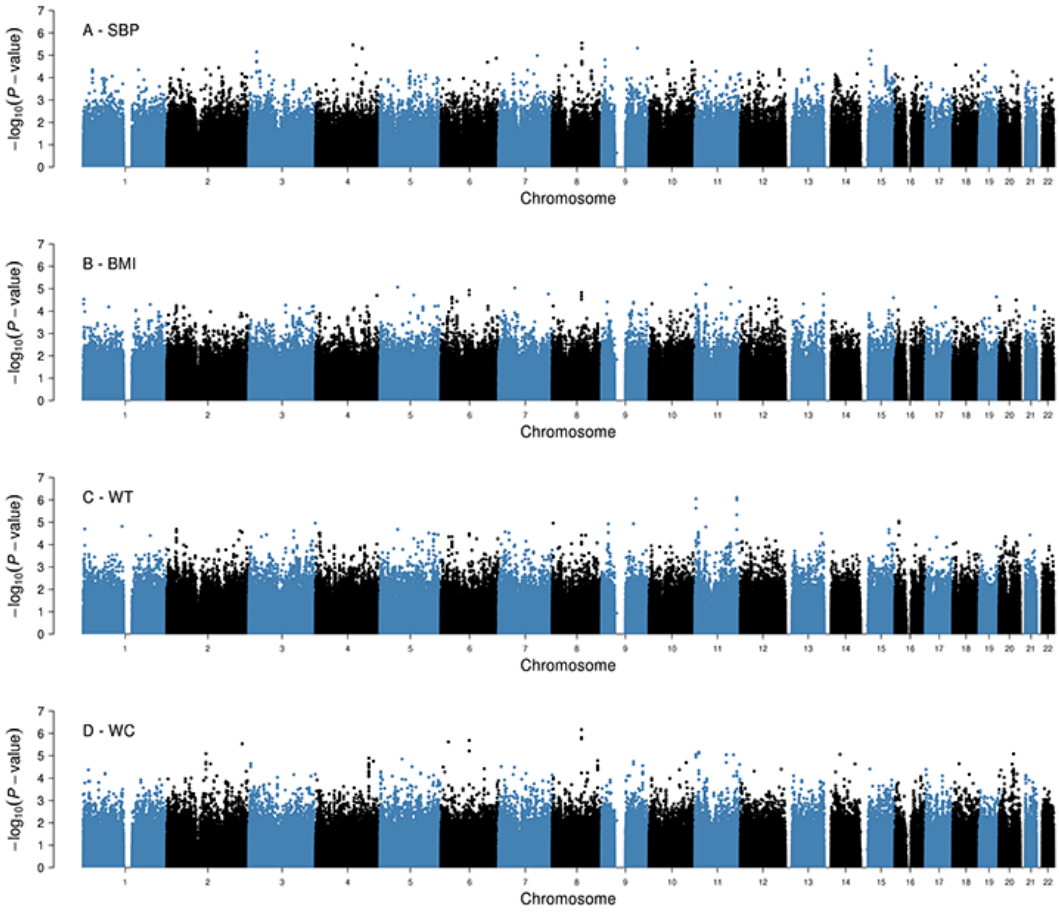

Figure S4. Genome-wide association tests for dominance effects for 4 quantitative traits in the combined sample of EGCUT and LL cohorts. These traits are a) SBP (systolic blood pressure), b) BMI (body mass index), c) WT (weight), and d) WC (waist circumference)**.** Plotted are -log10 of *p*-values for dominance effects from the analysis of fitting both additive and dominance effects.

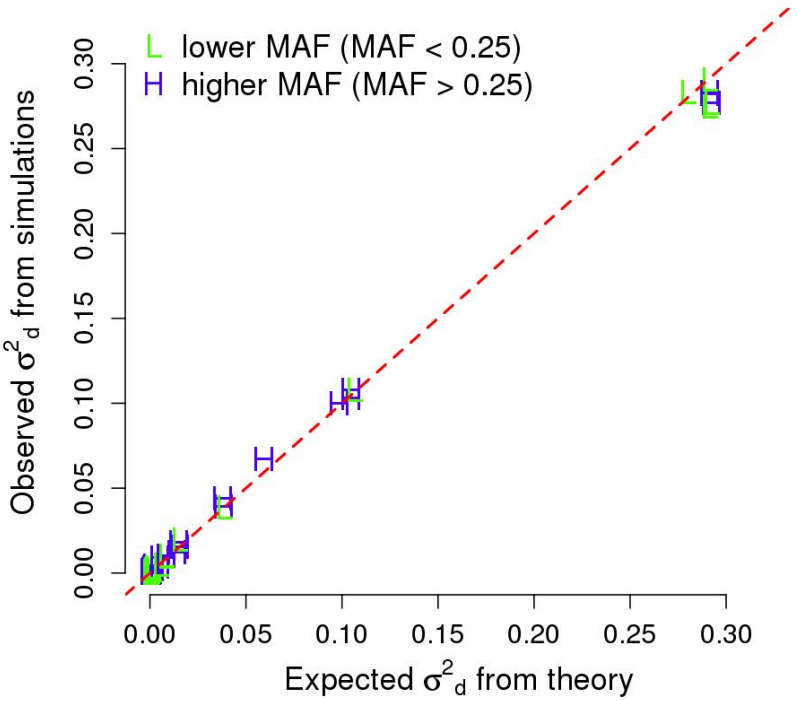

Figure S5. Plot of the observed σ^2_d from simulations against the expected σ^2_d from theory. In theory[1], dominance variance at a SNP equals dominance variance at a causal variant times r^4 with r being the LD correlation between the SNP and the causal variant, i.e. $\sigma^2_d = r^4\sigma^2_{d(\text{Causal})}$. To confirm this, we conducted simulations by extracting 1,000 proximal SNPs on chromosome 1 as a pool of causal variants (including 577 SNPs with MAF < 0.25 and 423 SNPs with MAF > 0.25) and one additional SNP (MAF = 0.18) as the observed SNP from the ARIC data set. For each of the causal variants, we generated a quantitative phenotype using the same simulation approach as in **Appendix** with $\sigma^2_{a(\text{Causal})} / \sigma^2_P = 0.3$ and $\sigma^2_{d(\text{Causal})} / \sigma^2_P = 0.3$ with σ^2_P being the phenotypic variance, and estimated σ^2_d from an association analysis of the observed SNP and simulated phenotype using Equation 5. The LD between the observed SNP and the causal variants is a function of MAF difference between the SNP and causal variants, which causes variation in σ^2_d.

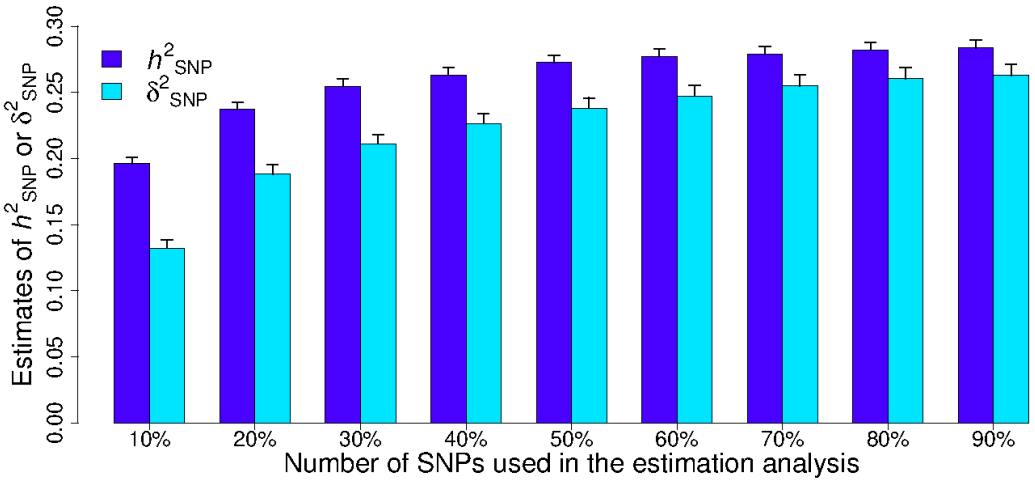

Figure S6. Estimates of h^2_{SNP} and δ^2_{SNP} based on a range of numbers of SNPs from simulations. Simulation strategy can be found in the **Appendix.** In brief, we randomly sampled 10% of SNPs as a pool of "unobserved causal variants", and used the remaining 90% as the "observed SNPs". We gradually reduced the LD between the observed SNPs and the unobserved causal variants by including a smaller number of "observed SNPs" in the GREMLd estimation analysis. Shown are the mean estimates over 100 simulations. Error bars are the standard errors of mean estimates.

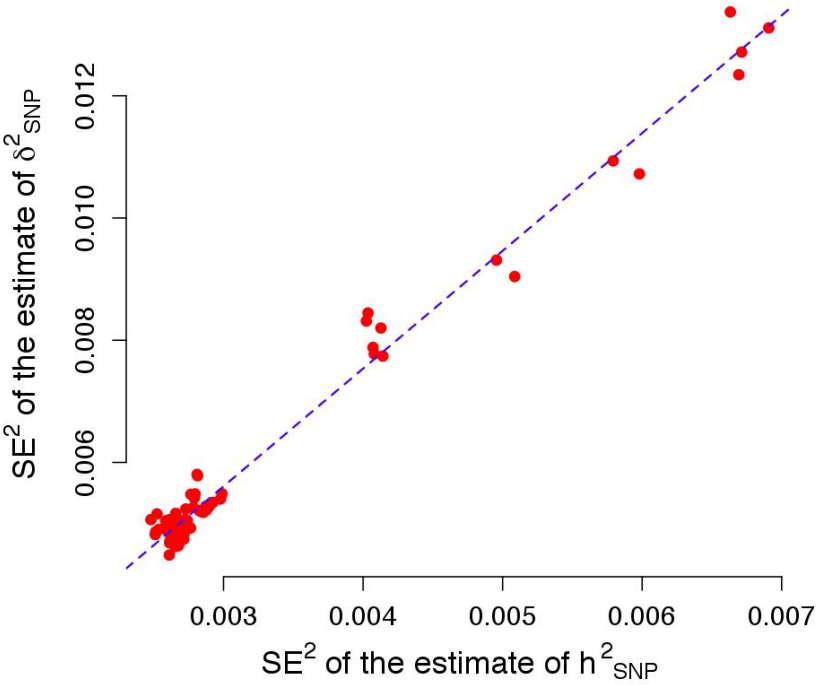

Figure S7. Plot of $\mathrm{SE}^2(\hat{h}^2_{SNP})$ against $\mathrm{SE}^2(\hat{\delta}^2_{SNP})$ for 79 traits in the ARIC cohort.

The blue dash line represents the fitted regression with a slope of 1.93. $\mathrm{SE}^2(\hat{h}^2_{SNP})$ and $\mathrm{SE}^2(\hat{\delta}^2_{SNP})$ are the estimates of $\mathrm{var}(\hat{h}^2_{SNP})$ and $\mathrm{var}(\hat{\delta}^2_{SNP})$, respectively.

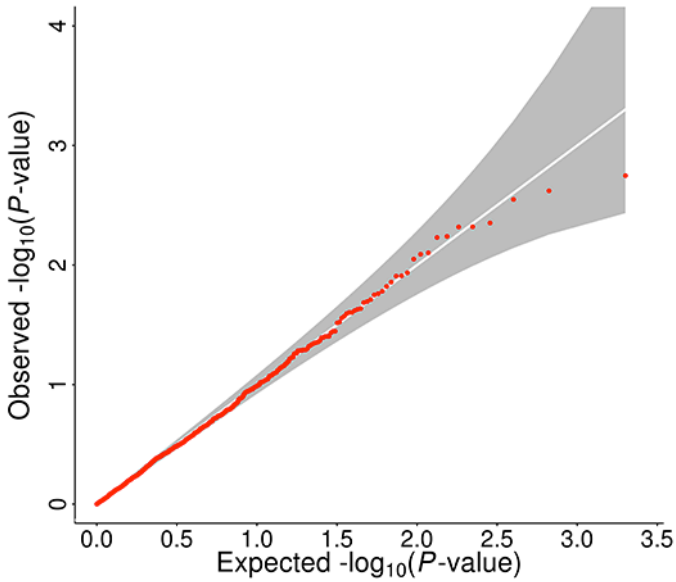

Figure S8. QQ-plot of *p*-values for dominance variation at an observed SNP from 1000 simulations where the underlying causal variant has a strong genetic effect that is purely additive. Genotypes of the causal variant and the SNP are generated from a bivariate binomial distribution, given simple size = 5,000, MAF = 0.4 for the causal variant, MAF = 0.2 for the SNP, and LD $r^2 = 0.25$. The phenotype is generated as such that additive variance at the causal variance explained 10% of the phenotypic variance, and the dominance variance is 0. Association test for dominance variance at the SNP is preformed based on the method described in Equation (3). The grey area shown on the figure is the 95% confidence interval.

Table S1. Genotyping and quality controls in the ARIC, EGCUT and Lifelines cohorts.

Cohort	Platform	Inclusion criteria				SNPs that met QC
		MAF	SNP call rate	Sample call rate	*p* for HWE	
ARIC	Affymetrix Genome-Wide Human SNP Array 6.0	≥ 1%	≥ 98%	≥ 98%	$> 10^{-3}$	593,521
EGCUT	Illumina Human370CNV	≥ 1%	≥ 95%	≥ 95%	$> 10^{-6}$	326,898
	Illumina OMNI-Express	≥ 1%	≥ 95%	≥ 95%	$> 10^{-6}$	633,182
Lifelines	Illumina Cyto SNP12 v2	≥ 1%	≥ 95%	≥ 95%	$> 10^{-6}$	245,943

p for HWE: *p*-value from Hardy-Weinberg Equilibrium test.

Table S2. Descriptive summary of the 79 quantitative traits in the ARIC cohort.

Group	Trait	Description (unit)	Mean (SD) in males	Mean (SD) in females
Height	Height	Height (cm)	176.2 (6.48)	162 (5.9)
	SitHT	Sitting height (cm)	92.8 (3.47)	86.4 (3.34)
Obesity	WT	Weight (lb)	187.5 (30.02)	153.7 (32.64)
	WT@25	Weight at the age of 25 (lb)	165.8 (26.05)	126.4 (19.87)
	BMI	Weight (kg) divided by squared height (m)	27.4 (3.98)	26.6 (5.49)
	WC	Waist circumference (cm)	99.6 (10.37)	93.1 (14.83)
	HC	Hip circumference (cm)	102.7 (7.54)	104.2 (10.86)
	WHR	Waist-to-hip ratio, the ratio of waist to hip	1 (0.05)	0.9 (0.08)
	WHRadjBMI	BMI adjusted WHR	0.8 (0.04)	0.7 (0.07)
	Wrist	Wrist breadth (mm)	57.8 (3.57)	49.8 (3.32)
	Calf	Calf circumference (cm)	38.2 (3.07)	36.7 (3.85)
	TRI	Triceps skinfold (mm)	19.6 (7.67)	28.9 (7.95)
	SUB	Subscapular skinfold (mm)	21.2 (8.16)	22.4 (10.22)
Lipoprotein	Apo	Apolipoprotein (mmol/L)	1.7 (1.13)	1.5 (0.94)
	ApoA	Apolipoprotein (mg/L)	1187.9 (248.74)	1417.7 (314.18)
	ApoB	Apolipoprotein B (mg/L)	958.6 (268.52)	919.6 (289.79)
	CHL	Cholesterol (mmol/L)	5.5 (0.99)	5.7 (1.1)
	HDL	High-density lipoprotein (mmol/L)	1.1 (0.32)	1.5 (0.44)
	HDL2	Subfraction of HDL cholesterol (mmol/L)	0.3 (0.15)	0.4 (0.24)
	HDL3	Subfraction of HDL cholesterol (mmol/L)	0.8 (0.25)	1 (0.27)
	LDL	LDL cholesterol(mmol/L)	3.6 (0.92)	3.5 (1.03)
Diabetes	Glucose	Glucose (mmol/L)	6 (1.64)	5.7 (1.7)
	Insulin	Insulin (pmol/L)	91.1 (120.1)	78.2 (122.21)
Blood pressure	SBP	Systolic blood pressure (mmHg)	120.1 (16.09)	116.9 (17.54)
	BBP	Brachial systolic blood pressure (mmHg)	130.4 (18.81)	123.4 (20.41)
	ABP	Ankle systolic blood pressure (mmHg)	151.1 (22.37)	135.8 (22.93)
	ABPI	Ankle-brachial index, the ratio of ABP to BBP	1.2 (0.14)	1.1 (0.14)
	DBP	Diastolic blood pressure (mmHg)	73.6 (10.01)	69.8 (9.73)
Blood phenotypes	Ht	Hematocrit, the volume percentage (%) of red blood cells in blood	44.7 (2.94)	40 (2.86)
	Hb	Hemoglobin	15 (1.01)	13.3 (1)
	WBC	White blood cells count $\times 1000/mm^3$	6.5 (2.08)	6.2 (1.88)
	PRO	Blood proteins (gm/dl)	7.2 (0.39)	7.2 (0.41)
	Albumin	Albumin (gm/dl)	3.9 (0.24)	3.9 (0.25)
	FI	Factor I	294 (61.37)	299.4 (60.52)
	FVII	Factor VII	111.5 (24.54)	125.2 (30.97)
	FVIII	Factor VIII	122.8 (33.56)	127.4 (34.41)
	vWF	von Willebrand factor	113.5 (43.23)	111.4 (42.46)
	Na	Sodium (mmol/L)	140.9 (2.32)	140.9 (2.41)
	K	Potassium (mmol/L)	4.6 (0.44)	4.5 (0.48)
	Ca	Calcium (mg/dl)	1.2 (0.16)	1 (0.14)
	Mg	Magnesium (meq/L)	9.7 (0.40)	9.8 (0.42)
	P	Phosphorus (meq/L)	1.7 (0.15)	1.6 (0.15)

	Creatine	Serum creatine (mg/dl)	3.2 (0.44)	3.6 (0.46)
	UA	Uric acid (mg/dl)	6.7 (1.33)	5.3 (1.34)
Carotid artery	Lopamx	Maximum far wall width (L common carotid: opt ang)	0.8 (0.25)	0.7 (0.21)
	Lanamx	Maximum far wall width (L common carotid: anterior angle)	0.8 (0.24)	0.7 (0.19)
	Lpoamx	Maximum far wall width (L common carotid: pst ang)	0.8 (0.27)	0.7 (0.20)
	Ropamx	Maximum far wall width (R common carotid: opt ang)	0.8 (0.25)	0.7 (0.21)
	Ranamx	Maximum far wall width (R common carotid: an ang)	0.8 (0.22)	0.7 (0.19)
	Rpoamx	Maximum far wall width (R common carotid: pst ang)	0.8 (0.25)	0.7 (0.19)
	Rbiamx	Maximum far wall width (R bifurcation)	1.2 (0.69)	1.0 (0.52)
	Lopaav	Average far wall width (L common carotid: opt ang)	0.7 (0.19)	0.6 (0.16)
	Lanaav	Average far wall width (L common carotid: anterior angle)	0.7 (0.18)	0.6 (0.15)
	Lpoaav	Average far wall width (L common carotid: pst ang)	0.7 (0.19)	0.6 (0.16)
	Ropaav	Average far wall width (R common carotid: opt ang)	0.7 (0.19)	0.6 (0.15)
	Ranaav	Average far wall width (R common carotid: ant ang)	0.7 (0.18)	0.6 (0.15)
	Rpoaav	Average far wall width (R common carotid: pst ang)	0.7 (0.19)	0.6 (0.14)
	Rbiaav	Average far wall width (R bifurcation)	0.9 (0.45)	0.8 (0.34)
	Lopada	Average far wall thickness (L opt)	0.7 (0.17)	0.6 (0.15)
	Ropada	Average far wall thickness (R opt)	0.7 (0.17)	0.6 (0.14)
	Lbiada	Derived average far wall thickness (L bifurcation)	0.9 (0.33)	0.8 (0.26)
	Rbiada	Derived average far wall thickness (R bifurcation)	0.9 (0.37)	0.8 (0.29)
	Linada	Derived average far wall thickness (L internal carotid)	0.7 (0.28)	0.7 (0.26)
	Rinada	Derived average far wall thickness (R internal carotid)	0.8 (0.35)	0.7 (0.28)
	MeanDA	Mean of the derived average far wall thickness variables	0.8 (0.20)	0.7 (0.17)
	Lopart	Derived average far wall thickness (L opt)	0.7 (0.17)	0.6 (0.15)
	Ropart	Derived average far wall thickness (R opt)	0.6 (0.17)	0.6 (0.13)
	Lbiart	Derived average far wall thickness (L bifurcation)	0.9 (0.33)	0.8 (0.26)
	Rbiart	Derived average far wall thickness (R bifurcation)	0.9 (0.37)	0.8 (0.28)
	Linart	Derived average far wall thickness (L internal carotid)	0.7 (0.28)	0.6 (0.25)
	Rinart	Derived average far wall thickness (R internal carotid)	0.8 (0.34)	0.7 (0.28)
	MeanRT	Mean of the derived average far	0.8 (0.20)	0.7 (0.16)

		wall thickness variables		
Heart function	HR	Heart rate	66.1 (9.95)	69 (9.43)
	HR(ECG)	HR measured by electrocardiography (ECG)	64.9 (10.03)	68 (9.65)
	QT	Q-T interval	408.5 (28.75)	411.7 (27.82)
	PR	P-R interval	167.3 (24.98)	160.5 (24.53)
	QRS	QRS complex, the combination of three of the graphical deflection, Q, R, and S waves.	101.6 (12.79)	94.5 (11.16)
	Cor	Cornell voltage	13.1 (5.10)	10 (4.24)
Smoking	CIG	Cigarette smoking, average number of cigarettes per day times the number of years smoked	470.8 (492.07)	230.2 (350.77)

Table S3. Estimates of variance explained by additive and dominance variation at all SNPs for the 79 traits in ARIC cohort.

Group	Trait	*n*	h^2_{SNP} (SE)	*P*	δ^2_{SNP} (SE)	*P*
Height	Height	6710	0.48 (0.05)	< 1E-16	0.02 (0.07)	3.78E-01
	SitHT	6704	0.39 (0.05)	8.55E-15	0.02 (0.07)	3.63E-01
Obesity	***WT**	**6709**	**0.18 (0.05)**	**2.14E-04**	**0.14 (0.07)**	**2.28E-02**
	WT@25	6698	0.22 (0.05)	6.23E-06	0.11 (0.07)	5.81E-02
	***BMI**	**6709**	**0.23 (0.05)**	**3.50E-06**	**0.15 (0.07)**	**1.67E-02**
	***WC**	**6707**	**0.17 (0.05)**	**3.06E-04**	**0.12 (0.07)**	**4.13E-02**
	HC	6706	0.17 (0.05)	4.55E-04	0.01 (0.07)	4.32E-01
	WHR	6704	0.18 (0.05)	1.36E-04	0.12 (0.07)	5.10E-02
	WHRadjBMI	6701	0.13 (0.05)	3.00E-03	0.00 (0.07)	4.93E-01
	Wrist	6709	0.26 (0.05)	9.81E-08	0.06 (0.07)	2.08E-01
	***Calf**	**6708**	**0.21 (0.05)**	**1.09E-05**	**0.12 (0.07)**	**3.67E-02**
	TRI	6708	0.19 (0.05)	1.25E-04	0.08 (0.07)	1.38E-01
	SUB	6689	0.23 (0.05)	2.81E-06	0.04 (0.07)	2.60E-01
Lipoprotein	Apo	6691	0.30 (0.05)	1.39E-09	-0.04 (0.07)	2.98E-01
	ApoA	6702	0.14 (0.05)	2.26E-03	-0.02 (0.07)	3.65E-01
	ApoB	6703	0.15 (0.05)	1.06E-03	0.01 (0.07)	4.34E-01
	CHL	6699	0.26 (0.05)	1.29E-07	0.02 (0.07)	3.79E-01
	HDL	6705	0.25 (0.05)	5.53E-07	-0.07 (0.07)	1.63E-01
	HDL2	6702	0.11 (0.05)	1.64E-02	0.08 (0.07)	1.12E-01
	HDL3	6704	0.20 (0.05)	4.47E-05	-0.13 (0.07)	2.59E-02
	LDL	6595	0.21 (0.05)	1.42E-05	0.01 (0.07)	4.48E-01
Diabetes	Glucose	6679	0.17 (0.05)	4.82E-04	-0.09 (0.07)	8.98E-02
	Insulin	6699	0.06 (0.05)	1.10E-01	0.05 (0.07)	2.34E-01
Blood pressure	***SBP**	**6711**	**0.21 (0.05)**	**1.71E-05**	**0.16 (0.07)**	**1.18E-02**
	BBP	6481	0.18 (0.05)	4.06E-04	0.10 (0.07)	7.81E-02
	***ABP**	**6481**	**0.16 (0.05)**	**7.78E-04**	**0.19 (0.07)**	**3.59E-03**
	ABPI	6472	0.06 (0.05)	1.09E-01	0.09 (0.07)	8.94E-02
	DBP	6710	0.21 (0.05)	3.66E-05	0.08 (0.07)	1.38E-01
Blood phenotypes	Ht	6692	0.16 (0.05)	9.22E-04	-0.07 (0.07)	1.55E-01
	Hb	6691	0.20 (0.05)	7.60E-05	-0.03 (0.07)	3.28E-01
	WBC	6695	0.26 (0.05)	6.61E-08	-0.04 (0.07)	3.01E-01
	PRO	6708	0.20 (0.05)	3.30E-05	0.00 (0.07)	5.00E-01
	Albumin	6709	0.11 (0.05)	1.73E-02	0.10 (0.07)	8.52E-02
	FI	6685	0.24 (0.05)	1.47E-06	0.02 (0.07)	3.84E-01
	FVII	6550	0.18 (0.05)	1.77E-04	-0.12 (0.07)	4.89E-02
	FVIII	6682	0.25 (0.05)	2.96E-07	-0.02 (0.07)	3.57E-01
	vWF	6684	0.35 (0.05)	3.69E-12	0.03 (0.07)	3.10E-01
	Na	6708	0.05 (0.05)	1.51E-01	0.06 (0.07)	2.09E-01
	K	6710	0.15 (0.05)	1.68E-03	-0.07 (0.07)	1.66E-01
	Ca	6706	0.12 (0.05)	1.02E-02	0.06 (0.07)	1.94E-01
	Mg	6710	0.07 (0.05)	8.78E-02	0.01 (0.07)	4.30E-01
	***P**	**6708**	**0.19 (0.05)**	**6.76E-05**	**0.13 (0.07)**	**2.68E-02**
	Creatine	6709	0.24 (0.05)	1.13E-06	0.06 (0.07)	1.97E-01
	UA	6709	0.25 (0.05)	1.42E-07	0.08 (0.07)	1.13E-01
Carotid artery	Lopamx	5278	0.04 (0.06)	2.57E-01	0.12 (0.09)	1.02E-01
	Lanamx	4432	0.08 (0.08)	1.42E-01	0.02 (0.10)	4.22E-01
	Lpoamx	4804	0.12 (0.07)	4.37E-02	0.01 (0.10)	4.61E-01
	Ropamx	5216	0.03 (0.06)	3.00E-01	0.11 (0.09)	1.09E-01

	Ranamx	4143	0.09 (0.08)	1.31E-01	0.04 (0.11)	3.71E-01
	Rpoamx	5199	0.05 (0.06)	2.36E-01	-0.03 (0.09)	3.81E-01
	Rbiamx	4048	-0.07 (0.08)	1.95E-01	0.01 (0.12)	4.81E-01
	Lopaav	5279	0.04 (0.06)	2.73E-01	0.15 (0.09)	5.57E-02
	Lanaav	4435	0.15 (0.08)	2.95E-02	0.02 (0.10)	4.29E-01
	Lpoaav	4805	0.16 (0.07)	1.41E-02	-0.01 (0.10)	4.48E-01
	Ropaav	5224	0.08 (0.06)	9.93E-02	0.05 (0.09)	2.68E-01
	Ranaav	4143	0.12 (0.08)	6.92E-02	-0.06 (0.11)	3.00E-01
	Rpoaav	5200	0.08 (0.06)	1.17E-01	0.00 (0.09)	4.99E-01
	Rbiaav	4050	0.07 (0.08)	2.13E-01	-0.04 (0.11)	3.60E-01
	Lopada	6350	0.02 (0.05)	3.34E-01	0.09 (0.08)	1.27E-01
	Ropada	6352	0.10 (0.05)	3.09E-02	0.04 (0.07)	2.86E-01
	Lbiada	6341	0.15 (0.05)	3.10E-03	0.01 (0.07)	4.39E-01
	Rbiada	6345	0.03 (0.05)	3.17E-01	-0.11 (0.07)	6.96E-02
	Linada	6341	-0.02 (0.05)	3.72E-01	0.01 (0.07)	4.56E-01
	Rinada	6338	0.06 (0.05)	1.43E-01	-0.06 (0.07)	2.02E-01
	MeanDA	6351	0.09 (0.05)	4.91E-02	-0.05 (0.07)	2.57E-01
	Lopart	6350	0.03 (0.05)	2.85E-01	0.11 (0.08)	8.24E-02
	Ropart	6353	0.13 (0.05)	8.50E-03	0.07 (0.07)	1.58E-01
	Lbiart	6341	0.17 (0.05)	8.75E-04	0.03 (0.07)	3.23E-01
	Rbiart	6345	0.03 (0.05)	2.93E-01	-0.11 (0.07)	7.35E-02
	Linart	6343	0.01 (0.05)	4.30E-01	0.03 (0.07)	3.59E-01
	Rinart	6339	0.07 (0.05)	7.97E-02	-0.02 (0.07)	3.80E-01
	MeanRT	6351	0.12 (0.05)	1.41E-02	0.00 (0.07)	4.87E-01
Heart function	HR	6691	0.22 (0.05)	9.10E-06	0.06 (0.07)	1.83E-01
	***HR(ECG)**	**6611**	**0.20 (0.05)**	**3.69E-05**	**0.12 (0.07)**	**4.42E-02**
	QT	6616	0.23 (0.05)	3.23E-06	0.03 (0.07)	3.43E-01
	PR	6619	0.18 (0.05)	1.41E-04	0.01 (0.07)	4.39E-01
	QRS	6625	0.05 (0.05)	1.83E-01	0.06 (0.07)	1.78E-01
	Cor	6483	0.09 (0.05)	4.72E-02	-0.06 (0.07)	1.91E-01
Smoking	CIG	6636	0.14 (0.05)	4.26E-03	-0.03 (0.07)	3.23E-01

n = sample size; h^2_{SNP} = variance explained by additive variation at all SNPs; δ^2_{SNP} = variance explained by dominance variation at all SNPs; SE = standard error; P = p-value from a LRT test; * traits (in bold) with nominally significant estimates of δ^2_{SNP} ($P < 0.05$).

Table S4. Mean estimates of h^2_{SNP} and δ^2_{SNP} averaged over 100 simulations

	h^2	Est. h^2_{SNP} (SEM)	δ^2	Est. δ^2_{SNP} (SEM)
Scenario I	0.30	0.30 (0.01)	0.30	0.30 (0.01)
Scenario II		0.28 (0.01)		0.26 (0.01)

Scenario I: all the SNPs including the causal variants were included in the estimation analysis; Scenario II: causal variants were sampled from 10% of the SNPs and the other 90% of SNPs were used in the estimation analysis; h^2: variance explained by additive variation at the causal variants; δ^2: variance explained by dominance variation at the causal variants; Est.: mean estimate over 100 simulations; Est. h^2_{SNP} : variance explained by additive variation at all SNPs in the estimation analysis (all SNPs in Scenario I, all SNPs excluding causal variants in Scenario II); Est. δ^2_{SNP} : variance explained by dominance variation at all SNPs in the estimation analysis; SEM: standard error of the mean estimate.

Reference

1. Weir, B.S. (2008). Linkage disequilibrium and association mapping. Annu Rev Genomics Hum Genet 9, 129-142

Acknowledgements

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National HumanGenome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

EGCUT received funding through targeted financing from Estonian Government SF0180142s08, Estonian Research Roadmap through Estonian Ministry of Education and Research, and from Center of Excellence in Genomics (EXCEGEN), University of Tartu (SP1GVARENG), Estonian Research Council IUT2-2 grant and European Regional Development Fund.

The LifeLines Cohort Study, and generation and management of GWAS genotype data for the LifeLines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Economic Structure Enhancing Fund (FES) of the Dutch government, the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation. The

authors are grateful to the study participants, the staff from the LifeLines Cohort Study and the contributing research centers delivering data to LifeLines and the participating general practitioners and pharmacists. LifeLines Cohort Study: Behrooz Z Alizadeh (1), Rudolf A de Boer (2), H Marike Boezen (1), Marcel Bruinenberg (3), Lude Franke (4), Pim van der Harst (2), Hans L Hillege (1,2), Melanie M van der Klauw (5), Gerjan Navis (6), Johan Ormel (7), Dirkje S Postma (8), Judith GM Rosmalen (7), Joris P Slaets (9), Harold Snieder (1), Ronald P Stolk (1), Bruce HR Wolffenbuttel (5), Cisca Wijmenga (4)

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