

Supplementary Information

Genome-partitioning of genetic variation for complex traits using common SNPs

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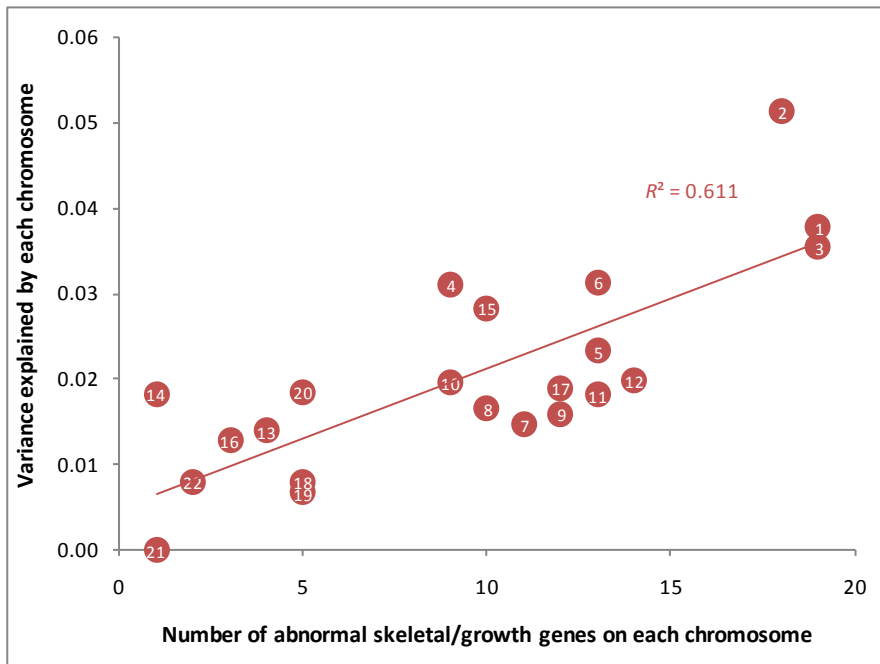
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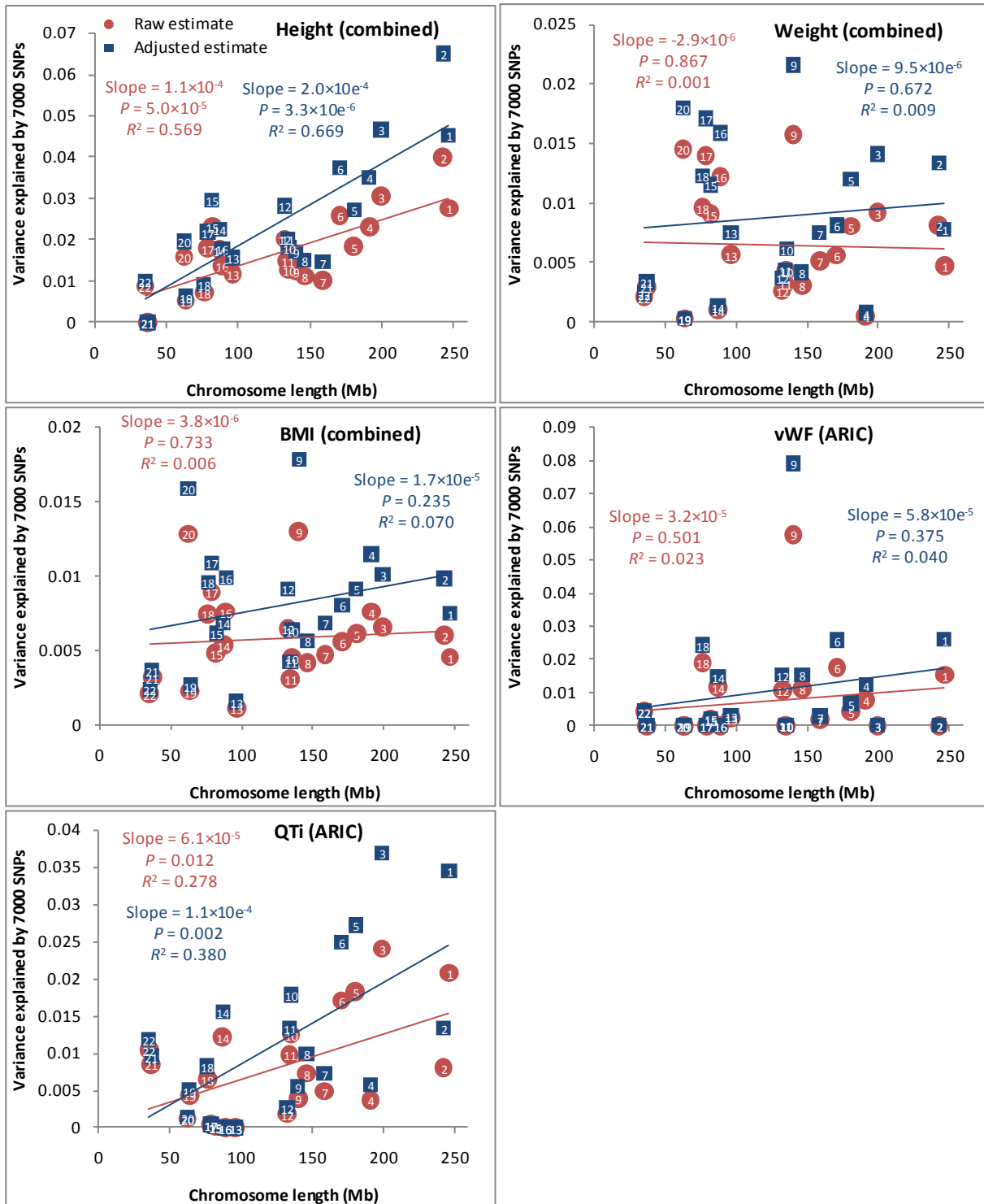
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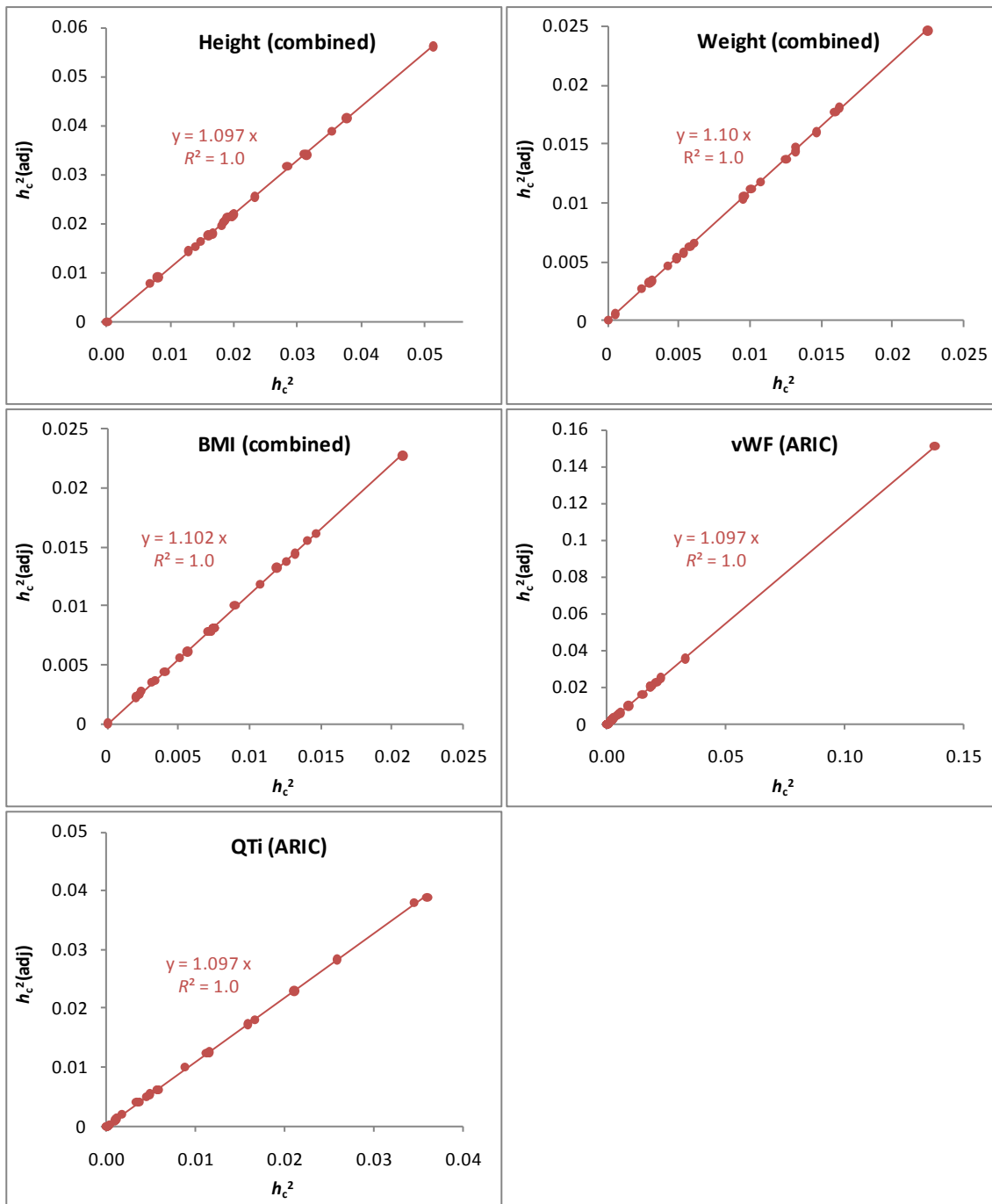
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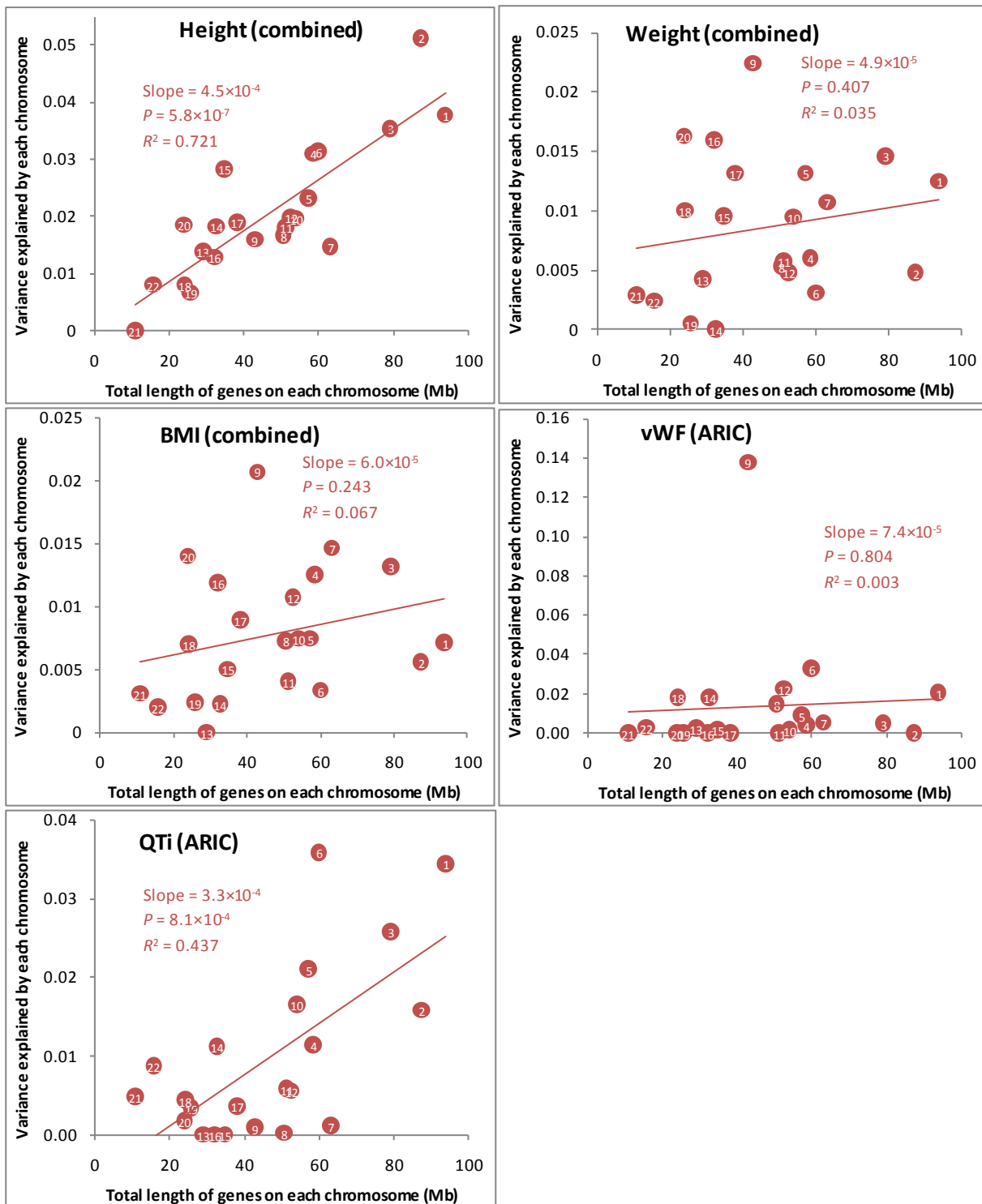
Supplementary Figure 1 Estimate of the variance explained by each chromosome (h_c^2) for height by the joint analysis using 11,586 unrelated individuals against the number of abnormal skeletal/growth genes on each chromosome (N_{asg}). The list of abnormal skeletal/growth genes were obtained from the **Supplementary Table 10** of the GIANT height paper¹. The estimate of h_c^2 for height is proportional to N_{asg} (regression $P = 1.7 \times 10^{-5}$). However, when we fit N_{asg} conditional on L_C by multiple regression, N_{asg} is not significant, $P(N_{asg} | L_C) = 0.260$, while L_C was significant fitted after N_{asg} , $P(L_C | N_{asg}) = 0.016$. Therefore, the linear relationship between h_c^2 and N_{asg} is more likely to be driven by the high correlation between N_{asg} and L_C ($r = 0.847$).



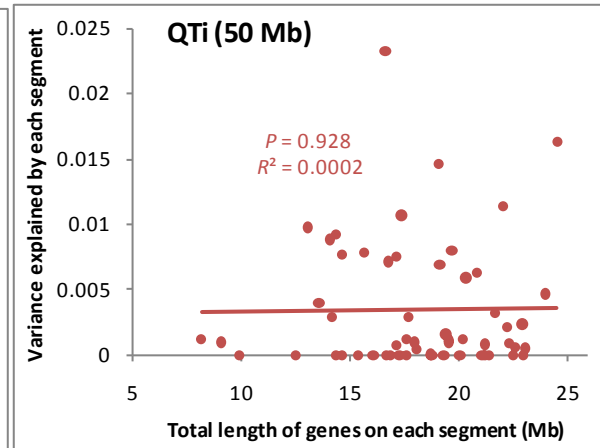
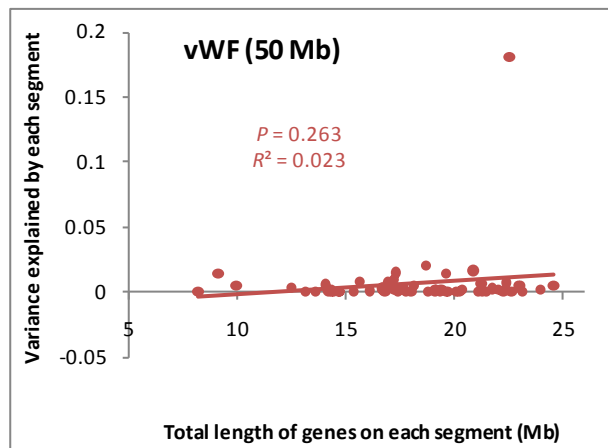
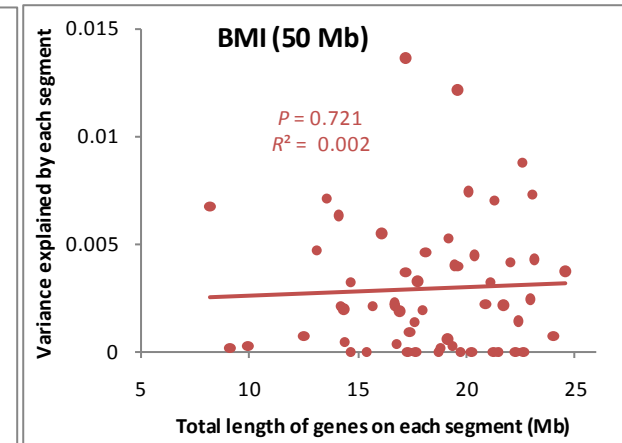
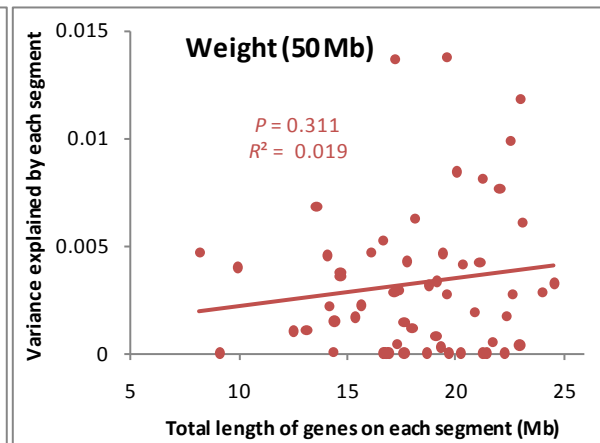
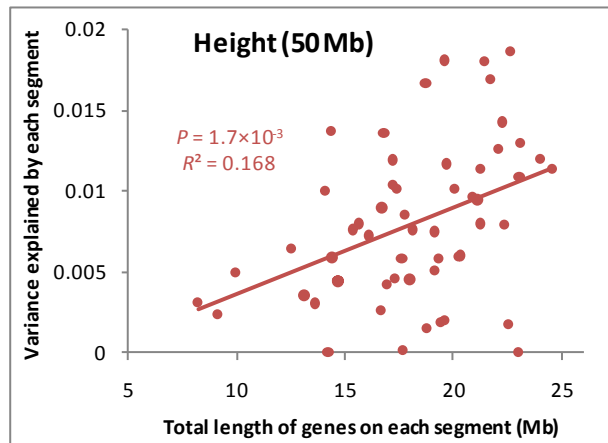
Supplementary Figure 2 Estimate of the variance explained by a subset of 7,000 SNPs on each chromosome for height, weight, BMI, vWF and QTc by the joint analysis using unrelated individuals against chromosome length. Adjusted estimate: adjusted for the error variance in estimating genetic relatedness due to the use of a finite number of SNPs. The slopes in red and blue refer to the raw and adjusted estimates, respectively.

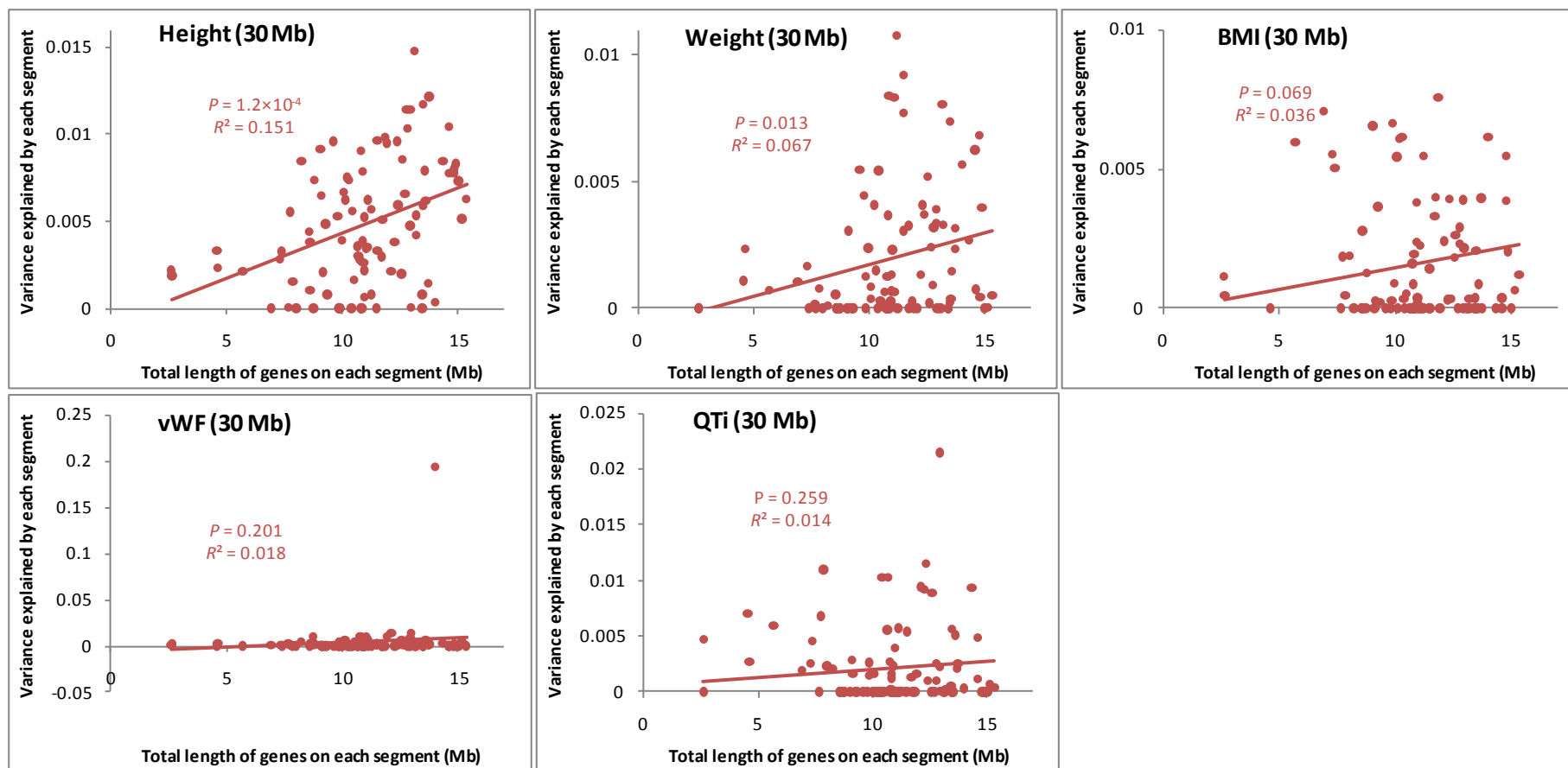


Supplementary Figure 3 Raw estimate of the variance explained by each chromosome (h_c^2) against the adjusted estimate for height, weight, BMI, vWF and QTl by the joint analysis using unrelated individuals. $h_c^2(\text{adj})$: the estimate was adjusted for the error variance in estimating genetic relatedness due to the use of a finite number of SNPs.

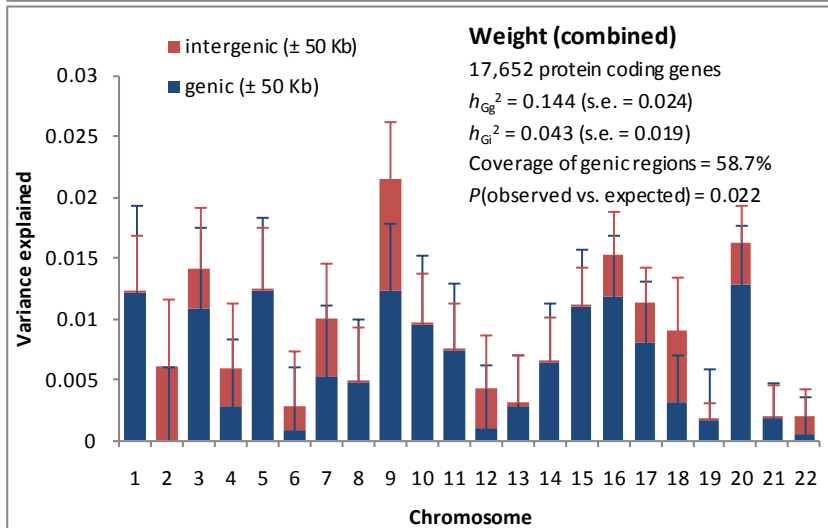
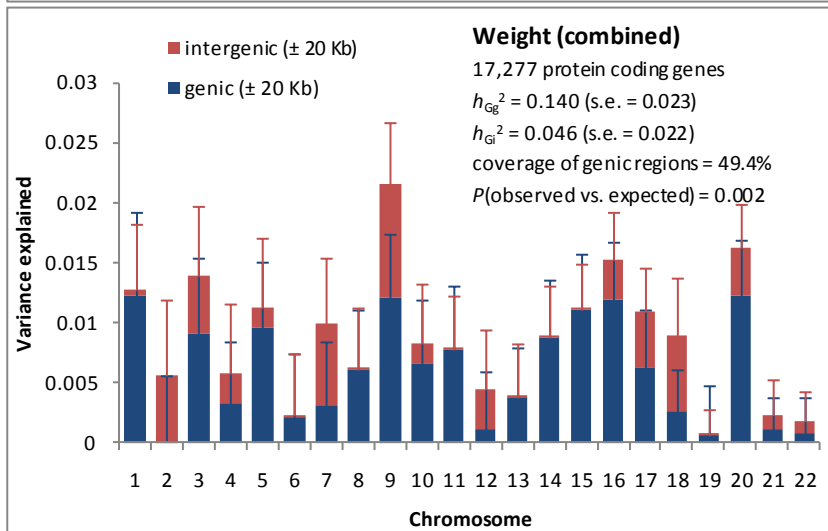
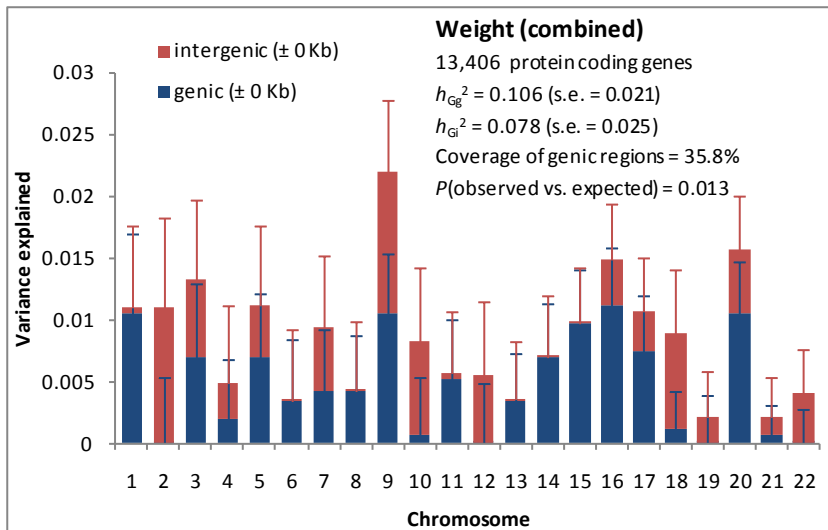


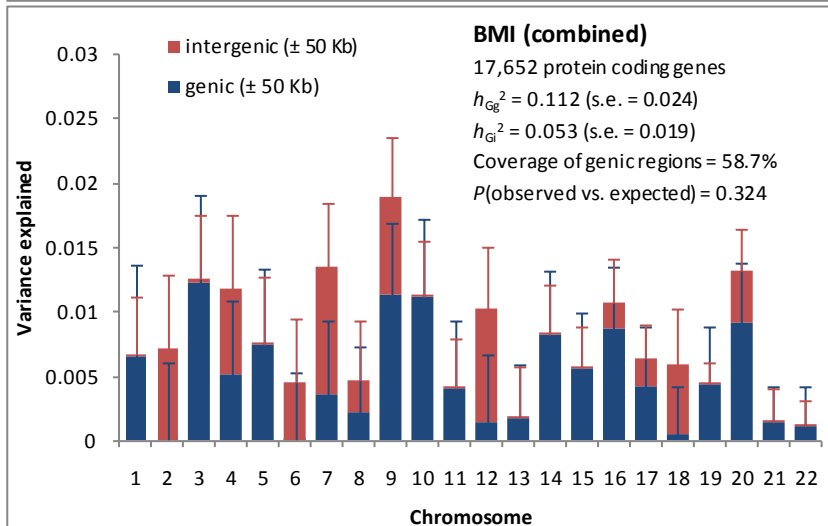
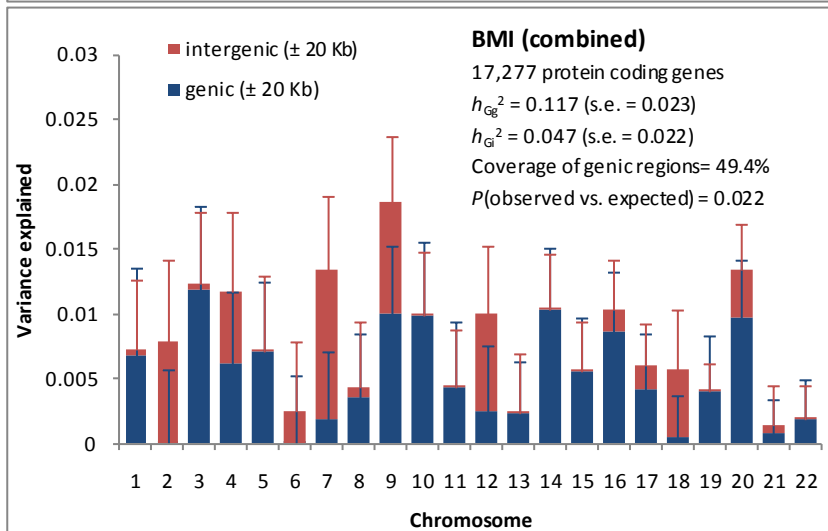
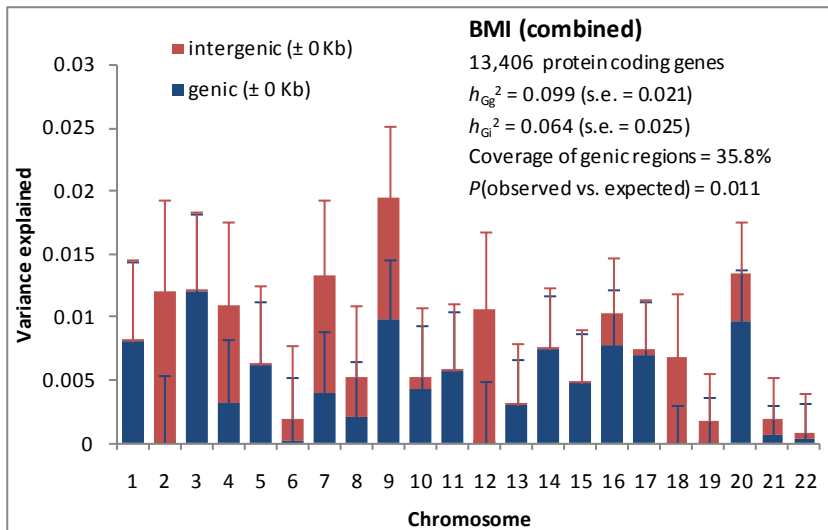
Supplementary Figure 4 Estimate of the variance explained by each chromosome for height, weight, BMI, vWF and QTc by the joint analysis using unrelated individuals against total gene length of each chromosome. The numbers in the circles/squares are the chromosome numbers.

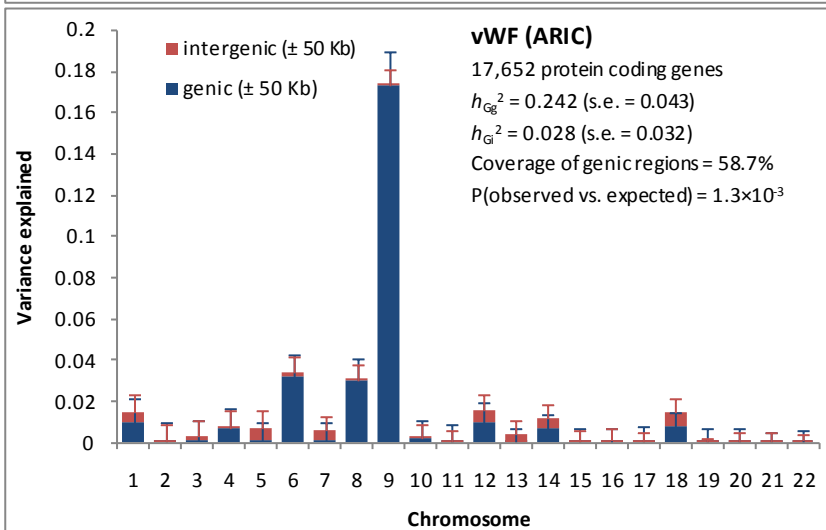
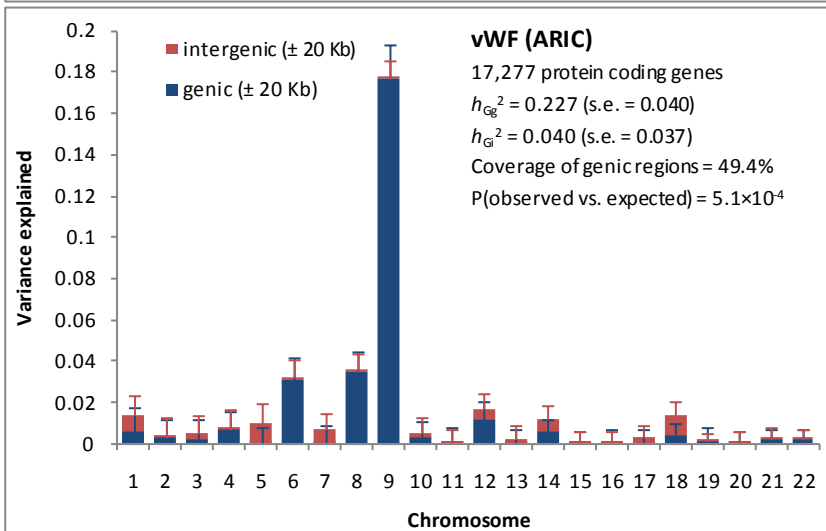
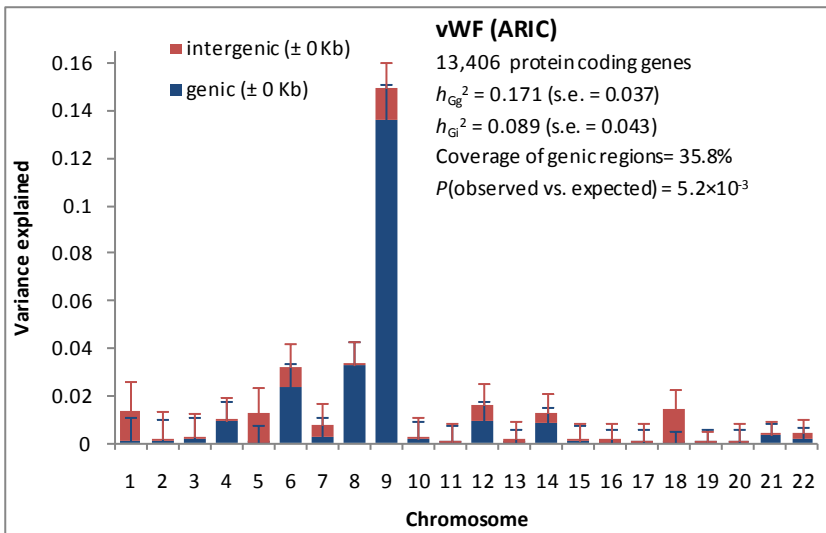


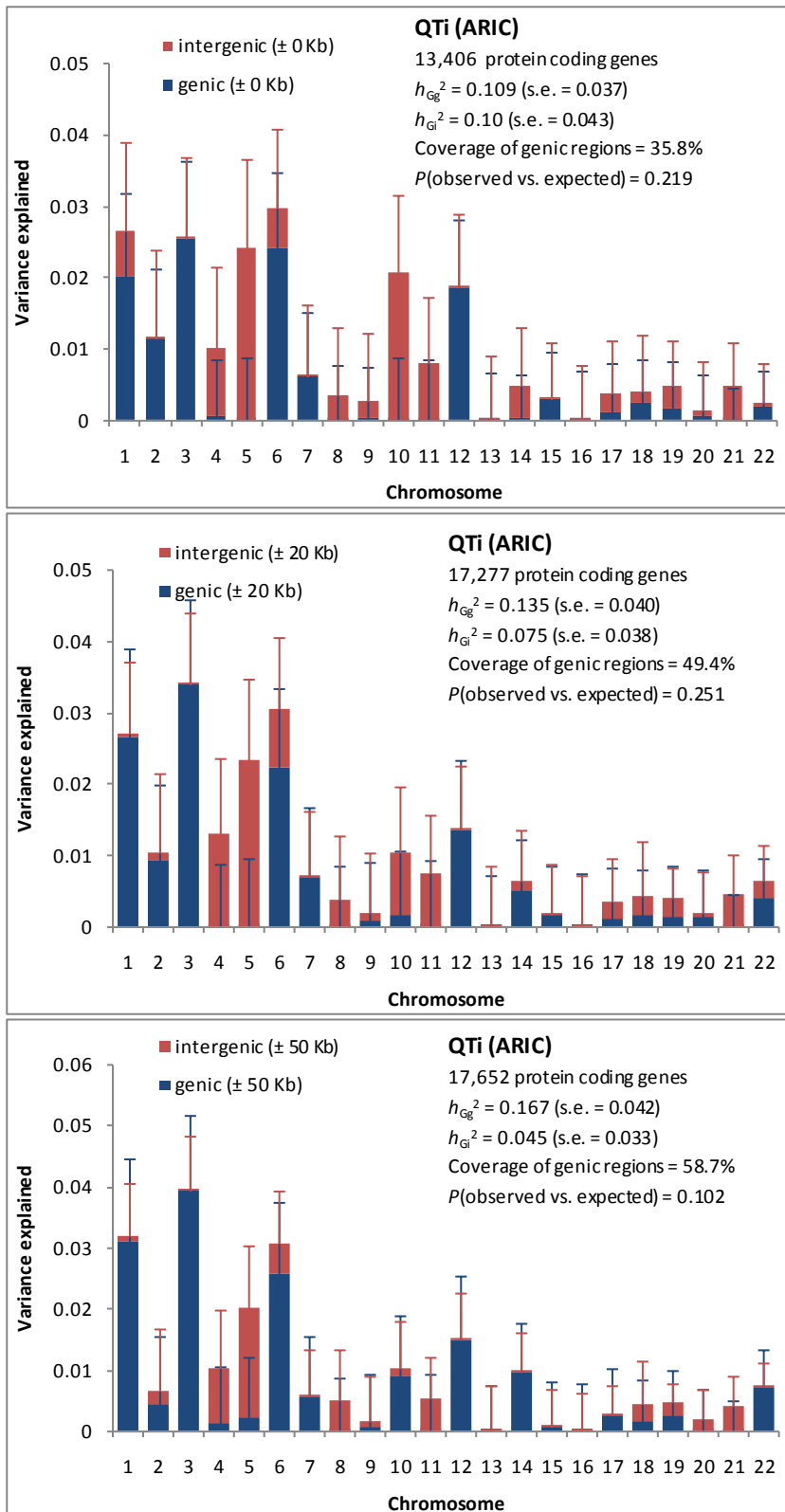


Supplementary Figure 5 Estimate of the variance explained by each genomic segment (50 or 30 Mb) for height, weight, BMI, vWF and QTc by the joint analysis using unrelated individuals against the total length of genes on each segment. Height, weight and BMI were analysed in the combined data set and vWF and QTc were analysed in the ARIC cohort.



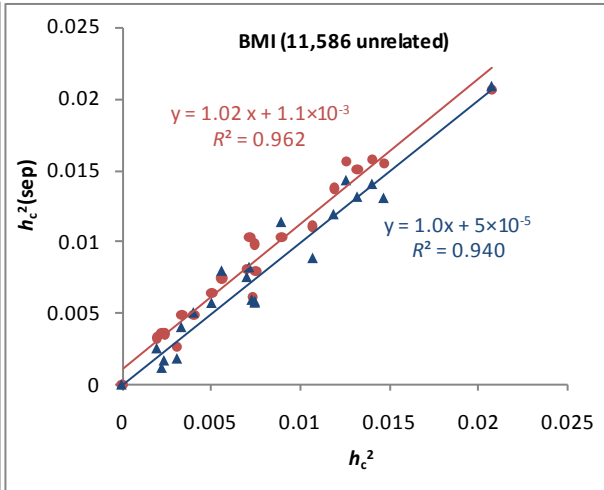
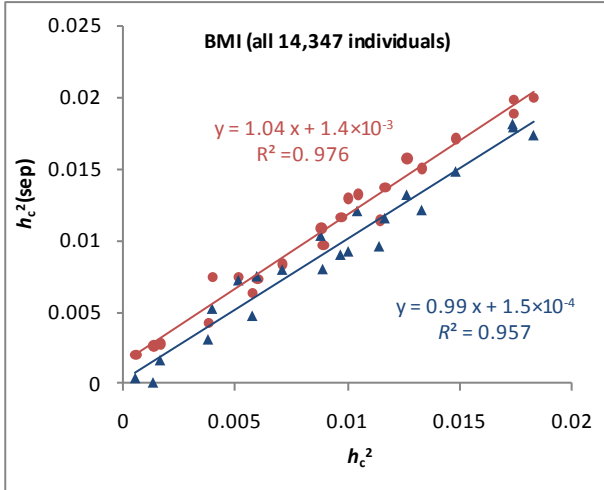
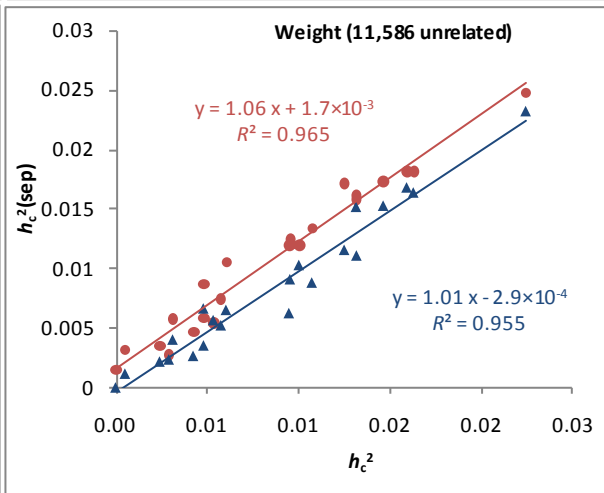
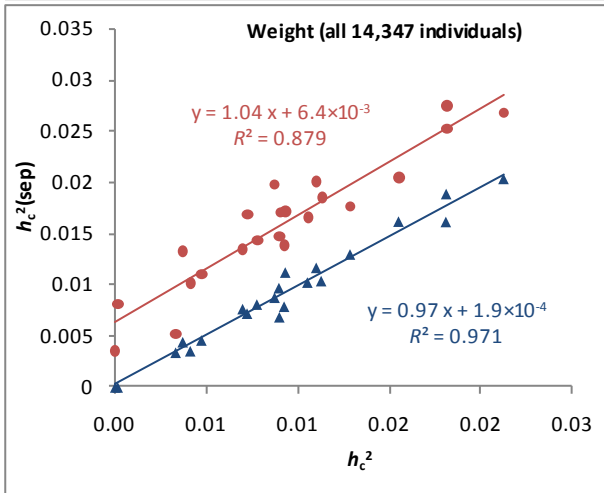
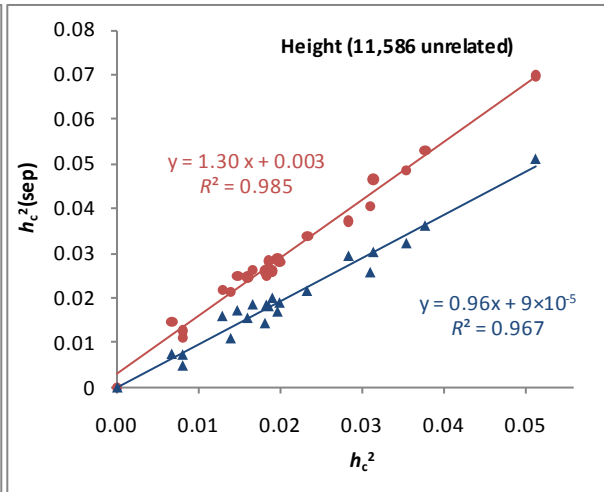
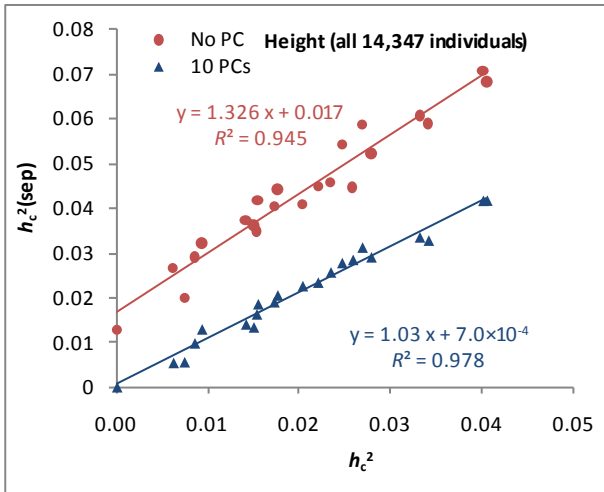


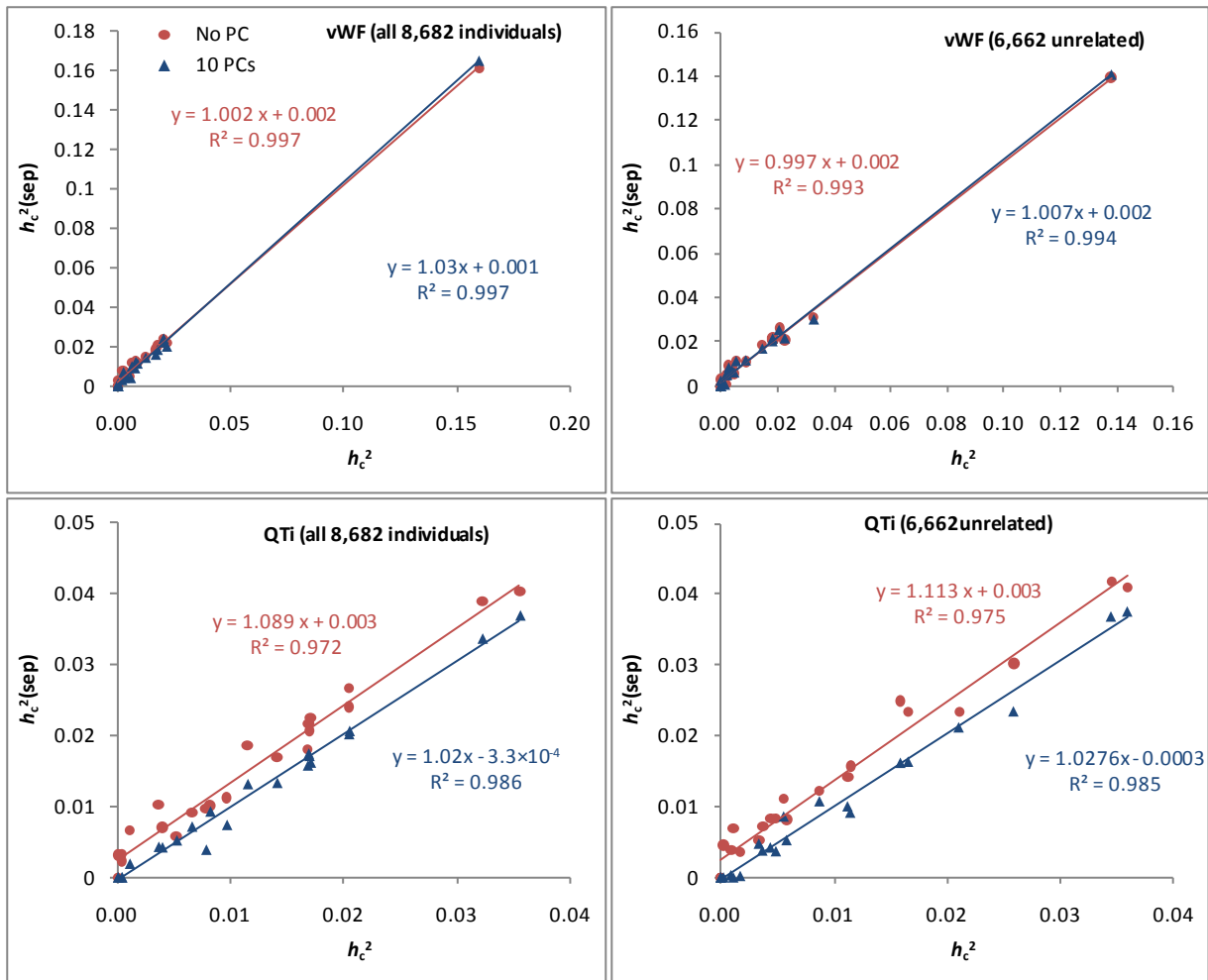




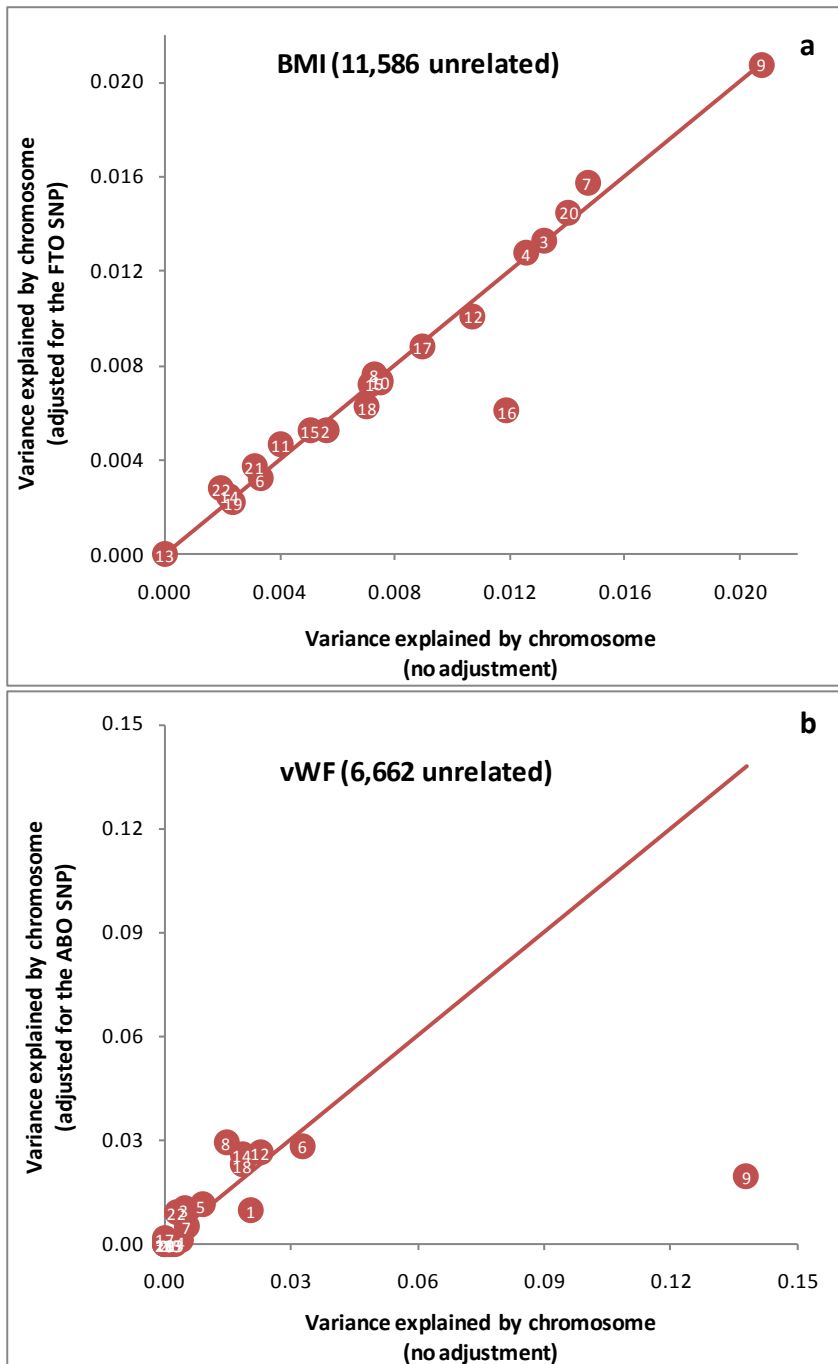
Supplementary Figure 6 Estimates of the variance explained by the genic and intergenic regions on each chromosome for weight, BMI, vWF and QTi by the joint analyses using unrelated individuals. Error bars are the standard errors of the estimates. h_{Gg}^2 and h_{Gi}^2 are the variances

explained by all the genic and intergenic SNPs across the whole genome. P (observed vs. expected):
goodness-of-fit test of the estimated h_{Gg}^2 / h_G^2 against that expected from the coverage of genic
regions.

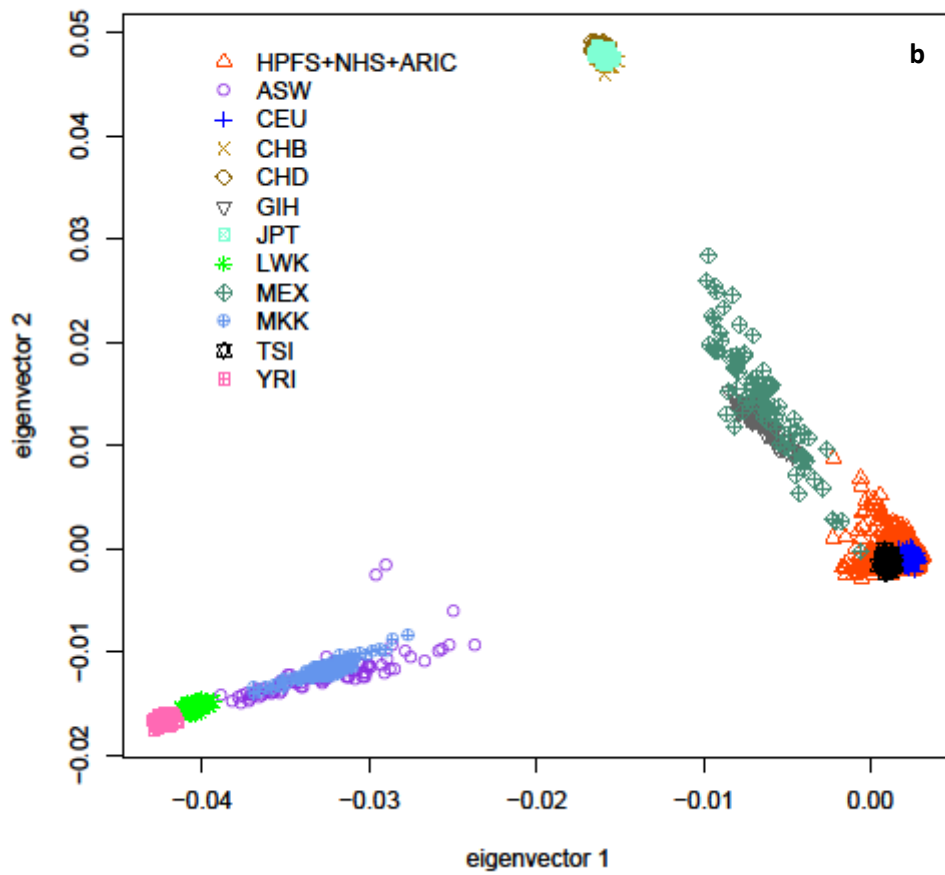
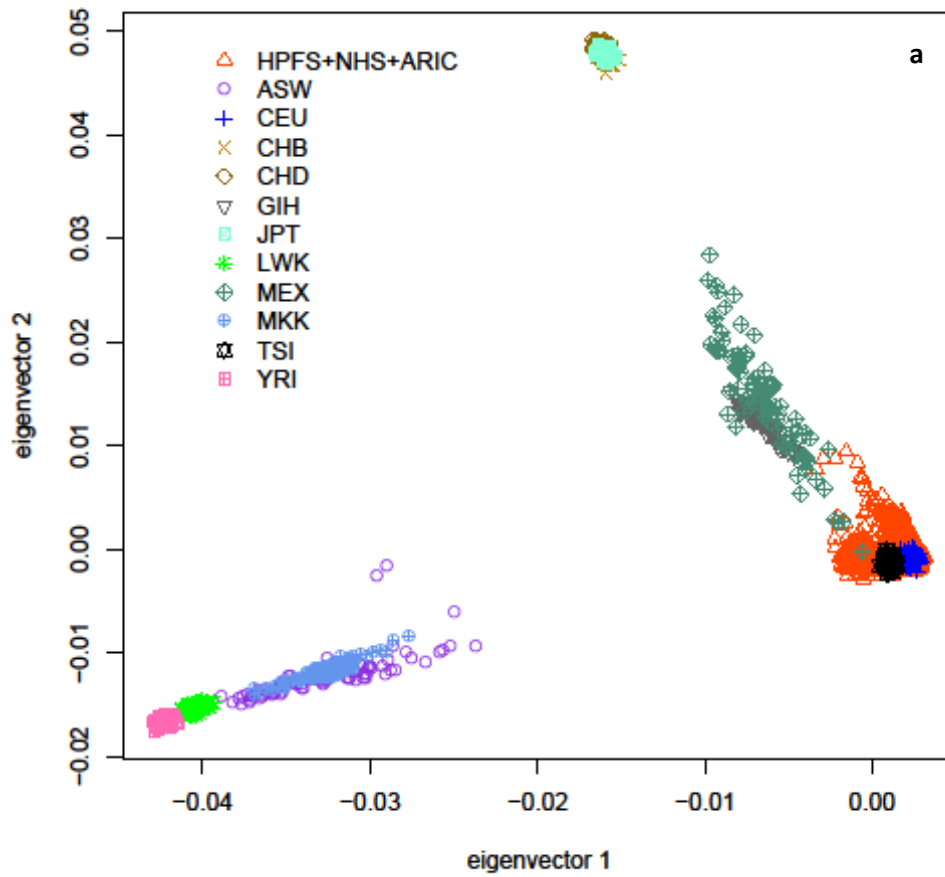




Supplementary Figure 7 Estimate of the variance explained by each chromosome for height, weight, BMI, vWF and QTl by the separate analyses ($h_c^2(\text{sep})$) against that by the joint analysis (h_c^2). 10 PCs: the first 10 eigenvectors from principal component analysis² were included as covariates when estimating $h_c^2(\text{sep})$.



Supplementary Figure 8 Estimates of the variance explained by chromosomes by the joint analysis with adjustment of the *FTO* SNP rs9939609 for BMI and the *ABO* SNP rs612169 for vWF against the estimates without adjustment. The straight line has a slope of 1.



Supplementary Figure 9 Principal component analysis (PCA) of ancestry. A total of 14,347 European Americans in the entire sample (HPFS+NHS+ARIC) were combined with 11 global

populations (1,397 individuals) from the Hapmap3 project. Population codes and samples sizes are as follows: ASW-African ancestry from Southwest USA, n=87; CEU-Utah residents with Northern and Western European ancestry from the CEPH collection, n=165; CHB-Han Chinese in Beijing, China, n=137; CHD-Chinese in Metropolitan Denver, Colorado, n=109; GIH-Gujarati Indians in Houston; Texas, n=101; JPT-Japanese in Tokyo, Japan, n=113; LWK-Luhya in Webuye, Kenya, n=110; MEX -Mexican ancestry in Los Angeles; California, n=86; MKK-Maasai in Kinyawa, Kenya, n=184; TSI-Tuscans, Italy, n=102; YRI- Yoruba in Ibadan, Nigeria n=203. PCA² was conducted on a total of 15,744 individuals using ~533K autosomal SNPs that were genotyped in common between the present and Hapmap3 studies. In panel **a**, the entire sample of 14,347 individuals in the present study are shown in the plot, and in panel **b**, a subset of 11,586 unrelated individuals are shown.

Supplementary Tables

Supplementary Table 1 Estimates of the variance explained by all autosomal SNPs for height, weight, BMI, vWF and QT_i in each cohort and in the combined data set.

		ARIC				HPFS & NHS				Combined			
		n	^a h_G^2	s.e.	P value	n	h_G^2	s.e.	P	n	h_G^2	s.e.	P value
Height	^b no PC	6,657	0.510	0.049	2.5×10^{-33}	5,072	0.470	0.063	3.0×10^{-19}	11,576	0.448	0.029	4.5×10^{-69}
	^c 4 PCs	6,657	0.448	0.050	1.8×10^{-20}	5,072	0.395	0.066	5.6×10^{-10}	11,576	0.421	0.030	8.9×10^{-49}
	^c 10 PCs	6,657	0.446	0.051	2.8×10^{-20}	5,072	0.380	0.067	4.9×10^{-9}	11,576	0.419	0.030	7.9×10^{-48}
	^c 20 PCs	6,657	0.445	0.051	2.8×10^{-20}	5,072	0.381	0.067	5.6×10^{-9}	11,576	0.416	0.030	1.2×10^{-46}
Weight	no PC	6,659	0.235	0.049	1.1×10^{-7}	5,054	0.227	0.064	6.1×10^{-5}	11,560	0.186	0.028	2.9×10^{-13}
	4 PCs	6,659	0.209	0.050	8.6×10^{-6}	5,054	0.206	0.065	5.9×10^{-4}	11,560	0.174	0.029	1.2×10^{-10}
	10 PCs	6,659	0.202	0.050	1.8×10^{-5}	5,054	0.197	0.066	1.2×10^{-3}	11,560	0.173	0.029	2.2×10^{-10}
	20 PCs	6,659	0.204	0.050	1.5×10^{-5}	5,054	0.185	0.067	2.4×10^{-3}	11,560	0.169	0.029	6.8×10^{-10}
BMI	no PC	6,657	0.231	0.050	8.2×10^{-7}	5,054	0.142	0.063	9.0×10^{-3}	11,558	0.165	0.029	3.0×10^{-10}
	4 PCs	6,657	0.222	0.051	3.2×10^{-6}	5,054	0.133	0.065	1.8×10^{-2}	11,558	0.159	0.029	5.2×10^{-9}
	10 PCs	6,657	0.208	0.051	1.5×10^{-5}	5,054	0.129	0.065	2.2×10^{-2}	11,558	0.159	0.029	5.3×10^{-9}
	20 PCs	6,657	0.212	0.051	1.0×10^{-5}	5,054	0.111	0.066	4.3×10^{-2}	11,558	0.158	0.029	8.7×10^{-9}
vWF	no PC	6,641	0.252	0.051	1.6×10^{-7}								
	4 PCs	6,641	0.252	0.051	2.3×10^{-7}								
	10 PCs	6,641	0.254	0.051	2.0×10^{-7}								
	20 PCs	6,641	0.256	0.051	1.9×10^{-7}								
QT _i	no PC	6,567	0.209	0.050	3.1×10^{-6}								
	4 PCs	6,567	0.170	0.051	4.4×10^{-4}								
	10 PCs	6,567	0.168	0.052	5.0×10^{-4}								
	20 PCs	6,567	0.166	0.052	6.0×10^{-4}								

^a estimate of variance explained by all the autosomal SNPs. ^b without PC adjustment. ^c adjustment by the first 4, 10 and 20 PCs from PCA.

Supplementary Table 2 Estimates of variance explained by chromosomes for height, weight, BMI, vWF and QT_i by the joint analysis using unrelated individuals. L_c : chromosome length, which is defined as the distance between the first and the last SNPs on each chromosome.

Chr.	L_c (Mb)	Height (combined)		Weight (combined)		BMI (combined)		vWF (ARIC)		QT _i (ARIC)	
		h_c^2	s.e.	h_c^2	s.e.	h_c^2	s.e.	h_c^2	s.e.	h_c^2	s.e.
1	246.42	0.0377	0.0088	0.0125	0.0081	0.0072	0.0080	0.0206	0.0143	0.0345	0.0153
2	242.56	0.0513	0.0094	0.0048	0.0077	0.0056	0.0077	0.0000	0.0136	0.0159	0.0148
3	199.30	0.0354	0.0084	0.0146	0.0080	0.0132	0.0079	0.0047	0.0122	0.0259	0.0142
4	191.11	0.0310	0.0079	0.0060	0.0071	0.0126	0.0076	0.0040	0.0118	0.0115	0.0128
5	180.54	0.0233	0.0078	0.0132	0.0074	0.0075	0.0072	0.0088	0.0120	0.0211	0.0132
6	170.64	0.0314	0.0079	0.0031	0.0065	0.0033	0.0066	0.0329	0.0127	0.0360	0.0138
7	158.67	0.0147	0.0069	0.0107	0.0071	0.0147	0.0073	0.0054	0.0115	0.0011	0.0118
8	146.11	0.0166	0.0068	0.0053	0.0065	0.0073	0.0066	0.0147	0.0112	0.0002	0.0104
9	140.15	0.0160	0.0067	0.0224	0.0071	0.0207	0.0070	0.1379	0.0169	0.0009	0.0109
10	135.19	0.0196	0.0071	0.0095	0.0069	0.0075	0.0068	0.0015	0.0111	0.0166	0.0122
11	134.25	0.0181	0.0064	0.0058	0.0061	0.0040	0.0062	0.0000	0.0105	0.0058	0.0110
12	132.26	0.0199	0.0067	0.0048	0.0064	0.0107	0.0067	0.0226	0.0119	0.0056	0.0116
13	96.18	0.0139	0.0061	0.0042	0.0057	0.0000	0.0055	0.0022	0.0094	0.0000	0.0105
14	87.01	0.0183	0.0060	0.0000	0.0052	0.0023	0.0053	0.0183	0.0099	0.0112	0.0099
15	81.88	0.0284	0.0064	0.0095	0.0054	0.0050	0.0051	0.0018	0.0088	0.0000	0.0088
16	88.66	0.0129	0.0058	0.0159	0.0061	0.0119	0.0059	0.0000	0.0093	0.0000	0.0097
17	78.61	0.0190	0.0060	0.0132	0.0058	0.0089	0.0054	0.0000	0.0085	0.0037	0.0088
18	76.11	0.0080	0.0054	0.0100	0.0056	0.0070	0.0054	0.0183	0.0099	0.0044	0.0093
19	63.57	0.0067	0.0045	0.0005	0.0043	0.0024	0.0045	0.0000	0.0070	0.0034	0.0074
20	62.37	0.0185	0.0058	0.0163	0.0055	0.0140	0.0054	0.0000	0.0086	0.0017	0.0084
21	36.88	0.0000	0.0037	0.0029	0.0038	0.0031	0.0039	0.0000	0.0062	0.0049	0.0069
22	35.13	0.0080	0.0040	0.0024	0.0039	0.0020	0.0040	0.0028	0.0064	0.0087	0.0073
Total	2783.60	0.4487		0.1880		0.1710		0.2967		0.2131	

Supplementary Table 3 Regression analyses of the estimate of variance explained by each chromosome (h_C^2) for height, weight, BMI, vWF and QT_i by the joint analysis using unrelated individuals on the number of genes on each chromosome ($N_{g(C)}$), chromosome length (L_C) and total length of genes on each chromosome ($L_{g(C)}$).

	Height (combined)			Weight (combined)			BMI (combined)			vWF (ARIC)			QT _i (ARIC)		
	Slope	P value	R ²	Slope	P value	R ²	Slope	P value	R ²	Slope	P value	R ²	Slope	P value	R ²
$L_{g(C)}$ (Mb)	4.5×10^{-4}	5.8×10^{-7}	0.721	4.9×10^{-5}	0.407	0.035	6.0×10^{-5}	0.243	0.067	9.2×10^{-7}	0.956	0.000	1.5×10^{-5}	0.011	0.283
L_C (Mb)	1.6×10^{-4}	1.4×10^{-6}	0.695	1.8×10^{-5}	0.402	0.035	2.3×10^{-5}	0.214	0.076	6.9×10^{-5}	0.524	0.021	1.2×10^{-4}	1.1×10^{-3}	0.422
$N_{g(C)}$	1.6×10^{-5}	7.9×10^{-3}	0.303	1.4×10^{-6}	0.671	0.009	1.1×10^{-6}	0.710	0.007	7.4×10^{-5}	0.803	0.003	3.3×10^{-4}	8.1×10^{-4}	0.437
$L_{g(C)} \mid N_{g(C)}$	4.9×10^{-4}	2.9×10^{-5}		6.4×10^{-5}	0.464		9.5×10^{-5}	0.206		1.1×10^{-4}	0.449		9.3×10^{-5}	0.028	
$L_C \mid N_{g(C)}$	1.5×10^{-4}	8.8×10^{-5}		2.0×10^{-5}	0.475		3.1×10^{-5}	0.206		1.3×10^{-4}	0.769		2.8×10^{-4}	0.030	
$L_{g(C)} \mid L_C$	3.7×10^{-4}	0.184		1.5×10^{-5}	0.952		-3.4×10^{-5}	0.874		-9.5×10^{-6}	0.663		5.7×10^{-6}	0.362	
$N_{g(C)} \mid L_C$	1.3×10^{-6}	0.790		-5.4×10^{-7}	0.900		-1.9×10^{-6}	0.605		-1.9×10^{-3}	0.116		2.6×10^{-4}	0.475	
$L_C \mid L_{g(C)}$	2.9×10^{-5}	0.768		1.3×10^{-5}	0.891		3.5×10^{-5}	0.655		-4.3×10^{-6}	0.861		3.3×10^{-6}	0.636	
$N_{g(C)} \mid L_{g(C)}$	-3.7×10^{-6}	0.480		-1.2×10^{-6}	0.812		-2.8×10^{-6}	0.508		7.5×10^{-4}	0.095		2.5×10^{-5}	0.852	

$L_C \mid N_{g(C)}$ represents regression of the estimate of h_C^2 on L_C conditional on $N_{g(C)}$. L_C is defined as the distance between the first and the last SNPs on each chromosome.

Supplementary Table 4 Regression analyses of the estimate of variance explained by each genomic segment (50 or 30 Mb) on the total length of genes ($L_{g(S)}$), the number of genes ($N_{g(S)}$), the total length of exons ($L_{ex(S)}$) and the number of exons ($N_{ex(S)}$) of each segment.

	Height (combined)			Weight (combined)			BMI (combined)			vWF (ARIC)			QTi (ARIC)		
	Slope	P value	R ²	Slope	P value	R ²	Slope	P value	R ²	Slope	P value	R ²	Slope	P value	R ²
50 Mb segments															
$L_{g(S)}$	5.4×10^{-4}	1.7×10^{-3}	0.168	1.3×10^{-4}	0.311	0.019	4.1×10^{-5}	0.721	0.002	9.9×10^{-4}	0.263	0.023	1.6×10^{-5}	0.928	0.000
$N_{g(S)}$	6.4×10^{-6}	0.131	0.042	1.9×10^{-6}	0.538	0.007	-1.1×10^{-6}	0.682	0.003	1.1×10^{-5}	0.608	0.005	-3.5×10^{-6}	0.423	0.012
$L_{ex(S)}$	9.6×10^{-3}	0.017	0.101	2.5×10^{-3}	0.392	0.014	-1.2×10^{-3}	0.656	0.004	1.5×10^{-2}	0.473	0.010	-2.0×10^{-3}	0.627	0.004
$N_{ex(S)}$	2.6×10^{-6}	0.017	0.101	8.9×10^{-7}	0.256	0.024	-8.6×10^{-8}	0.905	0.000	4.7×10^{-6}	0.400	0.013	-6.4×10^{-7}	0.576	0.006
$N_{g(S)} L_{g(S)}$	-1.7×10^{-8}	0.997		4.5×10^{-7}	0.897		-2.1×10^{-6}	0.500		-1.2×10^{-6}	0.959		-4.9×10^{-6}	0.332	
$L_{ex(S)} L_{g(S)}$	2.4×10^{-3}	0.634		9.5×10^{-4}	0.807		-3.2×10^{-3}	0.362		-9.6×10^{-4}	0.972		-4.1×10^{-3}	0.467	
$N_{ex(S)} L_{g(S)}$	7.9×10^{-7}	0.559		6.5×10^{-7}	0.528		-4.2×10^{-7}	0.653		1.2×10^{-6}	0.870		-1.2×10^{-6}	0.425	
$L_{g(S)} N_{g(S)}$	5.4×10^{-4}	6.5×10^{-3}		1.2×10^{-4}	0.420		8.5×10^{-5}	0.519		1.0×10^{-3}	0.323		1.2×10^{-4}	0.573	
$L_{g(S)} L_{ex(S)}$	4.7×10^{-4}	0.038		9.9×10^{-5}	0.556		1.3×10^{-4}	0.382		1.0×10^{-3}	0.394		1.3×10^{-4}	0.581	
$L_{g(S)} N_{ex(S)}$	4.6×10^{-4}	0.036		6.1×10^{-5}	0.709		8.4×10^{-5}	0.576		8.7×10^{-4}	0.452		1.4×10^{-4}	0.562	
30 Mb segments															
$L_{g(S)}$	5.2×10^{-4}	1.2×10^{-4}	0.151	2.5×10^{-4}	0.013	0.067	1.7×10^{-4}	0.069	0.036	1.0×10^{-3}	0.201	0.018	1.6×10^{-4}	0.259	0.014
$N_{g(S)}$	7.8×10^{-6}	0.020	0.058	3.0×10^{-6}	0.217	0.017	1.3×10^{-6}	0.578	0.003	2.1×10^{-5}	0.280	0.013	-2.0×10^{-6}	0.570	0.004
$L_{ex(S)}$	9.8×10^{-9}	1.9×10^{-3}	0.101	3.9×10^{-9}	0.095	0.030	1.5×10^{-9}	0.490	0.005	2.5×10^{-8}	0.173	0.020	-9.4×10^{-10}	0.778	0.001
$N_{ex(S)}$	2.6×10^{-6}	2.4×10^{-3}	0.097	1.2×10^{-6}	0.062	0.038	5.3×10^{-7}	0.376	0.009	8.0×10^{-6}	0.109	0.028	-3.9×10^{-7}	0.673	0.002
$N_{g(S)} L_{g(S)}$	1.7×10^{-6}	0.649		-1.9×10^{-7}	0.947		-1.2×10^{-6}	0.647		1.1×10^{-5}	0.629		-5.6×10^{-6}	0.172	
$L_{ex(S)} L_{g(S)}$	3.2×10^{-9}	0.432		3.5×10^{-11}	0.991		-2.1×10^{-9}	0.477		1.7×10^{-8}	0.499		2.9×10^{-4}	0.094	
$N_{ex(S)} L_{g(S)}$	8.3×10^{-7}	0.444		2.7×10^{-7}	0.743		-3.1×10^{-7}	0.690		6.7×10^{-6}	0.314		-6.3×10^{-9}	0.159	
$L_{g(S)} N_{g(S)}$	4.9×10^{-4}	2.0×10^{-3}		2.6×10^{-4}	0.031		2.0×10^{-4}	0.075		7.8×10^{-4}	0.403		3.5×10^{-4}	0.075	
$L_{g(S)} L_{ex(S)}$	4.3×10^{-4}	0.016		2.5×10^{-4}	0.065		2.3×10^{-4}	0.069		5.3×10^{-4}	0.621		-1.9×10^{-6}	0.122	
$L_{g(S)} N_{ex(S)}$	4.4×10^{-4}	0.013		2.2×10^{-4}	0.093		2.0×10^{-4}	0.104		3.2×10^{-4}	0.758		3.6×10^{-4}	0.062	

Supplementary Table 5 Estimates of the variance explained by the SNPs on the X-chromosome (h_x^2) for height, weight and BMI in the combined dataset and for vWF and QT_i in the ARIC cohort. h_x^2 is specified for females because the X-linked genetic variances are not the same for males and females under different assumptions of dosage compensation.

		n	h_x^2	s.e.	^a h_G^2	s.e.	^b LRT	^b P value
Height	Equal variance	11,576	0.0085	0.0046	0.446	0.029	4.64	0.0156
	No dosage compensation	11,576	0.0096	0.0057	0.446	0.029	3.66	0.0278
	Full dosage compensation	11,576	0.0061	0.0032	0.448	0.029	4.83	0.0140
Weight	Equal variance	11,560	0.0115	0.0051	0.187	0.028	6.50	0.0054
	No dosage compensation	11,560	0.0124	0.0063	0.186	0.028	4.72	0.0149
	Full dosage compensation	11,560	0.0089	0.0036	0.188	0.029	7.87	0.0025
BMI	Equal variance	11,558	0.0103	0.0049	0.165	0.029	5.94	0.0074
	No dosage compensation	11,558	0.0106	0.0060	0.165	0.028	4.08	0.0217
	Full dosage compensation	11,558	0.0082	0.0035	0.166	0.029	7.36	0.0033
vWF	Equal variance	6,641	0.0078	0.0077	0.258	0.050	3.22	0.036
	No dosage compensation	6,641	0.0084	0.0098	0.257	0.050	2.85	0.046
	Full dosage compensation	6,641	0.0057	0.0052	0.260	0.050	3.43	0.032
QT _i	Equal variance	6,567	0.0	0.0071	0.208	0.049	0.57	0.226
	No dosage compensation	6,567	0.0	0.0092	0.208	0.049	0.57	0.226
	Full dosage compensation	6,567	0.0	0.0048	0.208	0.049	0.57	0.226

^a h_G^2 : variance explained by all the autosomal SNPs. ^b likelihood test (LRT) statistic and its corresponding P value to test the null hypothesis of $h_x^2 = 0$.

Supplementary Table 6 Estimates of the variance explained by all autosomal SNPs under the assumptions of dosage compensation for height, weight and BMI in the combined dataset and for vWF and QT_i in the ARIC dataset.

		n	^a h_G^2	s.e.	^b LRT	^b P value
Height	Equal variance	11,576	0.448	0.029	307.16	4.5×10^{-69}
	No dosage compensation	11,576	0.369	0.026	228.02	8.1×10^{-52}
	Full dosage compensation	11,576	0.223	0.020	199.61	1.3×10^{-45}
Weight	Equal variance	11,560	0.186	0.028	51.94	2.9×10^{-13}
	No dosage compensation	11,560	0.148	0.028	30.89	1.4×10^{-8}
	Full dosage compensation	11,560	0.097	0.017	40.64	9.1×10^{-11}
BMI	Equal variance	11,558	0.165	0.029	38.32	3.0×10^{-10}
	No dosage compensation	11,558	0.124	0.028	20.79	2.6×10^{-6}
	Full dosage compensation	11,558	0.089	0.017	31.34	1.1×10^{-8}
vWF	Equal variance	6,641	0.252	0.051	26.07	1.6×10^{-7}
	No dosage compensation	6,641	0.156	0.043	13.43	1.2×10^{-4}
	Full dosage compensation	6,641	0.104	0.028	15.72	3.7×10^{-5}
QT _i	Equal variance	6,567	0.209	0.050	20.44	3.1×10^{-6}
	No dosage compensation	6,567	0.150	0.044	11.98	2.7×10^{-4}
	Full dosage compensation	6,567	0.078	0.026	11.30	3.9×10^{-4}

^a h_G^2 : variance explained by all the autosomal SNPs specified for females. ^b likelihood test (LRT) statistic and its corresponding *P* value to test the null hypothesis of $h_G^2 = 0$.

Supplementary Table 7 Study-specific descriptive statistics

Study	Trait	Year	Males						Females					
			n	mean	SD	median	min	max	n	mean	SD	median	min	max
NHS	Age (yrs)	1986-1988							3,265	55.75	6.76	56.25	41.50	67.75
	Height (cm)	1986-1988							3,261	1.64	0.061	1.63	1.35	1.83
	Weight (kg)	1990							3,010	73.79	16.25	70.31	40.82	154.22
	Weight (kg)	1992							3,192	74.03	16.18	70.76	40.82	163.29
	Weight (kg)	1994							3,060	75.15	16.59	72.57	39.92	150.14
	BMI (kg / m ²)	1990							3,010	27.47	5.74	26.52	15.81	54.87
	BMI (kg / m ²)	1992							3,192	27.54	5.73	26.57	14.98	54.87
	BMI (kg / m ²)	1994							3,060	27.95	5.89	27.10	14.98	54.87
HPFS	Age (yrs)	1976	2,400	59.17	8.41	59.71	43.16	77.25						
	Height (cm)	1976	2,398	1.79	0.065	1.78	1.55	2.03						
	Weight (kg)	1988	2,085	85.06	13.97	82.92	50.02	163.18						
	Weight (kg)	1990	2,039	85.63	14.33	83.53	54.43	161.42						
	Weight (kg)	1992	2,049	85.67	14.65	83.75	52.20	165.42						
	BMI (kg / m ²)	1988	2,085	26.60	3.80	26.0	16.30	46.20						
	BMI (kg / m ²)	1990	2,039	26.78	3.90	26.20	16.40	50.20						
	BMI (kg / m ²)	1992	2,049	26.76	4.0	26.10	16.50	49.40						
ARIC	Age (yrs)	1987-1989	4,081	54.67	5.67	55.0	44.0	66.0	4,601	53.95	5.68	54.0	44.0	66.0
	Height (m)	1987-1989	4,079	1.76	0.064	1.76	1.54	1.99	4,593	1.62	0.059	1.62	1.37	1.87
	Weight (kg)	1987-1989	4,078	85.32	13.54	84.09	50.45	182.27	4,595	69.77	14.85	66.82	36.36	141.82
	BMI (kg / m ²)	1987-1989	4,078	27.43	3.94	26.89	17.31	56.26	4,591	26.57	5.46	25.43	14.38	54.73
	Age (yrs)	1990-1992	3,938	57.57	5.66	58.00	47.0	68.0	4,440	56.89	5.65	57.0	47.0	69.0
	Weight (kg)	1990-1992	3,932	85.96	13.86	84.55	48.18	157.27	4,432	70.92	15.20	68.18	32.73	156.36
	BMI (kg / m ²)	1990-1992	3,932	27.63	4.04	27.07	16.46	57.33	4,427	27.01	5.57	25.95	13.66	55.85
	Age (yrs)	1993-1995	3,602	60.63	5.63	61.0	50.0	71.0	4,090	59.96	5.63	60.0	50.0	72.0
	Height (m)	1993-1995	3,597	1.76	0.064	1.76	1.54	2.00	4,087	1.61	0.059	1.61	1.36	1.85
	Weight (kg)	1993-1995	3,595	87.04	14.56	85.45	40.0	187.27	4,086	72.36	15.76	69.55	33.64	151.82
	BMI (kg / m ²)	1993-1995	3,595	28.13	4.30	27.55	14.52	59.11	4,086	27.78	5.85	26.70	13.30	57.34
	Age (yrs)	1996-1998	3,259	63.46	5.64	63.0	53.0	74.0	3,729	62.78	5.60	62.0	53.0	75.0
	Height (m)	1996-1998	3,250	1.76	0.065	1.76	1.53	1.99	3,725	1.61	0.059	1.61	1.39	1.82
	Weight (kg)	1996-1998	3,253	87.75	14.81	85.91	36.36	168.18	3,726	73.09	15.99	70.45	35.91	156.36
	BMI (kg / m ²)	1996-1998	3,249	28.45	4.39	27.86	13.52	53.08	3,725	28.14	5.93	27.06	14.95	55.62
	% vWF antigen	1987-1989	4,067	113.17	43.44	106.00	29.00	456.00	4,582	111.15	42.62	104.00	24.00	417.00
	QTi (ms)	1987-1989	4,030	408.66	28.71	407.00	285.00	564.00	4,533	411.78	27.85	410.00	310.00	556.00

Supplementary Table 8 Repeatability model analyses of height, weight and BMI in the ARIC and the HPFS & NHS cohorts.

	ARIC			NHS & HPFS	
	Height	Weight	BMI	Weight	BMI
n	6,657	6,659	6,657	5,054	5,054
$\sigma_{PE}^2 / \sigma_P^2$	0.483	0.713	0.710	0.726	0.807
s.e	0.048	0.047	0.048	0.062	0.061
σ_G^2 / σ_P^2	0.507	0.224	0.220	0.222	0.136
s.e	0.048	0.047	0.048	0.062	0.061
Repeatability	0.989	0.937	0.930	0.947	0.944
LRT	143.04	26.42	22.84	14.96	5.50
P value	2.9×10^{-33}	1.4×10^{-7}	8.8×10^{-7}	5.5×10^{-5}	9.5×10^{-3}

σ_{PE}^2 : variance of permanent environment effects. σ_G^2 : genetic variance attributed to all the autosomal SNPs. σ_P^2 : phenotypic variance. Repeatability = $(\sigma_G^2 + \sigma_{PE}^2) / \sigma_P^2$. The likelihood test (LRT) statistic and its corresponding *P* value is to test the null hypothesis of $\sigma_G^2 = 0$.

Supplementary Table 9 Estimates of the variance explained by genotype-sex interaction effects for height, weight, BMI, vWF and QT_i in each cohort and in the combined dataset.

		n	^a h_G^2	s.e	^b $h_{G \times S}^2$	s.e	^c LRT	^c P value
ARIC	Height	6,657	0.467	0.068	0.088	0.096	0.85	0.178
	Weight	6,659	0.237	0.069	0.0	0.095	0.0	0.50
	BMI	6,657	0.193	0.070	0.076	0.097	0.63	0.213
	vWF	6,641	0.247	0.068	0.011	0.089	0.02	0.450
	QT_i	6,567	0.208	0.069	0.003	0.096	0.002	0.482
HPFS & NHS	Height	5,072	0.358	0.093	0.204	0.126	2.67	0.051
	Weight	5,054	0.231	0.093	0.0	0.129	0.0	0.50
	BMI	5,054	0.111	0.093	0.060	0.129	0.20	0.327
Combined	Height	11,576	0.431	0.040	0.032	0.053	0.36	0.275
	Weight	11,560	0.165	0.040	0.041	0.055	0.55	0.229
	BMI	11,558	0.129	0.040	0.071	0.056	1.58	0.104

^a h_G^2 : variance explained by all the autosomal SNPs. ^b $h_{G \times S}^2$: variance explained by the genotype-sex interaction effects. ^c likelihood test (LRT) statistic and its corresponding *P* value to test the null hypothesis of $h_{G \times S}^2 = 0$.

Supplementary Table 10 Estimates of the variance explained by all autosomal SNPs for height, weight, BMI, vWF and QT_i in each gender group.

			Males			Females			^b Heterogeneity
			n	^a h_G^2	s.e.	n	h_G^2	s.e.	P value
ARIC	Height	^c no PC	3,159	0.590	0.10	3,498	0.633	0.092	0.756
		^d 10 PCs	3,159	0.460	0.105	3,498	0.563	0.096	0.469
	Weight	no PC	3,160	0.281	0.10	3,499	0.209	0.092	0.599
		10 PCs	3,160	0.250	0.103	3,499	0.162	0.095	0.531
	BMI	no PC	3,159	0.242	0.103	3,498	0.304	0.095	0.662
		10 PCs	3,159	0.236	0.104	3,498	0.280	0.096	0.756
	vWF	no PC	3,154	0.021	0.101	3,487	0.391	0.092	0.007
		10 PCs	3,154	0.055	0.102	3,487	0.367	0.094	0.024
	QT _i	no PC	3,117	0.313	0.104	3,450	0.144	0.092	0.223
		10 PCs	3,117	0.252	0.108	3,450	0.105	0.094	0.303
HPFS & NHS	Height	no PC	1,953	0.478	0.156	3,119	0.649	0.100	0.356
		10 PCs	1,953	0.339	0.167	3,119	0.522	0.107	0.358
	Weight	no PC	1,937	0.0	0.156	3,117	0.374	0.105	0.046
		10 PCs	1,937	0.0	0.169	3,117	0.376	0.107	0.060
	BMI	no PC	1,937	0.0	0.166	3,117	0.308	0.105	0.117
		10 PCs	1,937	0.0	0.175	3,117	0.330	0.107	0.107
Combined	Height	no PC	5,056	0.440	0.062	6,520	0.527	0.050	0.271
		10 PCs	5,056	0.371	0.065	6,520	0.485	0.052	0.166
	Weight	no PC	5,041	0.226	0.062	6,519	0.213	0.050	0.868
		10 PCs	5,041	0.207	0.064	6,519	0.196	0.051	0.892
	BMI	no PC	5,040	0.189	0.063	6,518	0.220	0.050	0.701
		10 PCs	5,040	0.184	0.065	6,518	0.211	0.051	0.748

^a variance explained by all the autosomal SNPs. ^b genetic heterogeneity P value between males and females by t-test. ^c without PC adjustment. ^d adjustment of the first 10 PCs from PCA.

Supplementary Table 11 Estimates of the variance explained by all autosomal SNPs for height, weight and BMI in Type-II diabetes (T2D) cases and controls separately in the HPFS & NHS cohorts.

		T2D cases (HPFS & NHS)			Control (HPFS & NHS)			^b Heterogeneity
		n	^a h_G^2	s.e.	n	h_G^2	s.e.	P value
Height	^c no PC	2,289	0.344	0.134	2,722	0.562	0.109	0.207
	^d 10 PCs	2,289	0.239	0.144	2,722	0.386	0.119	0.431
Weight	no PC	2,277	0.209	0.138	2,716	0.332	0.118	0.501
	10 PCs	2,277	0.158	0.145	2,716	0.224	0.125	0.731
BMI	no PC	2,277	0.129	0.135	2,716	0.198	0.121	0.703
	10 PCs	2,277	0.064	0.144	2,716	0.197	0.124	0.482

^a variance explained by all the autosomal SNPs. ^b genetic heterogeneity P value between T2D cases and controls by t-test. ^c without PC adjustment. ^d adjustment of the first 10 PCs from PCA.

Supplementary Table 12 Estimates of the variance explained by all the autosomal SNPs for height, weight and BMI in the combined dataset with and without the Type-II diabetes (T2D) cases.

		Combined			Combined (excluding T2D cases from the HPFS and NHS cohorts)		
		n	^a h_G^2	s.e.	n	h_G^2	s.e.
Height	^b no PC	11,576	0.448	0.029	9,348	0.468	0.035
	^c 10 PCs	11,576	0.419	0.030	9,348	0.427	0.037
Weight	no PC	11,560	0.186	0.028	9,344	0.198	0.035
	10 PCs	11,560	0.173	0.029	9,344	0.179	0.036
BMI	no PC	11,558	0.165	0.029	9,342	0.175	0.035
	10 PCs	11,558	0.159	0.029	9,342	0.172	0.036

^a variance explained by all the autosomal SNPs. ^b without PC adjustment. ^c adjustment of the first 10 PCs from PCA.

Supplementary Table 13 Estimates of the variance explained by all the autosomal SNPs for log-transformed height, weight and BMI in the combined dataset. The phenotypic correlation is 0.354 between height and weight, -0.034 between height and BMI and 0.917 between weight and BMI.

	Est.	s.e.
$\sigma_G^2(\log HT)$	5.8×10^{-4}	4.2×10^{-5}
$\sigma_G^2(\log WT)$	6.5×10^{-3}	9.8×10^{-4}
$\sigma_G^2(\log BMI)$	5.4×10^{-3}	8.6×10^{-4}
$\sigma_G(\log HT, \log WT)$	8.7×10^{-4}	3.3×10^{-4}
$\sigma_G(\log HT, \log BMI)$	-2.9×10^{-4}	3.3×10^{-4}
$\sigma_G(\log WT, \log BMI)$	4.8×10^{-3}	6.6×10^{-4}
$r_G(\log HT, \log WT)$	0.448	0.173
$r_G(\log HT, \log BMI)$	-0.164	0.186
$r_G(\log WT, \log BMI)$	0.808	0.131

logHT, log WT and logBMI represent log-transformation of height, weight and BMI respectively.

The genetic covariance between logHT and logWT is $\sigma_G(\log HT, \log WT) = \sigma_G^2(\log HT) + [\sigma_G^2(\log WT) - \sigma_G^2(\log BMI)] / 4$. The genetic correlation between logHT and logWT is defined as $r_G(\log HT, \log WT) = \sigma_G(\log HT, \log WT) / \sqrt{[\sigma_G^2(\log HT) \sigma_G^2(\log WT)]}$. The s.e. of the estimates of $\sigma_G^2(\log HT)$, $\sigma_G^2(\log WT)$ and $\sigma_G^2(\log BMI)$ were calculated from the REML analysis, and the s.e. of $\sigma_G(\log HT, \log WT)$ and $r_G(\log HT, \log WT)$ were calculated based upon the s.e. of $\sigma_G^2(\log HT)$, $\sigma_G^2(\log WT)$ and $\sigma_G^2(\log BMI)$.

Supplementary Note

Linear relationship between h_C^2 and L_C is irrespective of the number of SNPs

We randomly sampled 7,000 SNPs on each chromosome and estimated h_C^2 using the same number of SNPs for each chromosome in a joint analysis. Although the estimates for longer chromosomes slightly decreased because of poor tagging by using only 7,000 SNPs, the linear relationship between the estimate of h_C^2 and L_C remained for height ($P = 5.0 \times 10^{-5}$ and $R^2 = 0.569$) (**Supplementary Fig. 2**). We have demonstrated previously that the error variance of estimated genetic relationships using a finite number of SNPs is inversely proportional to the number of SNPs and the estimate of genetic variance after adjustment for sampling error is independent of the number of SNPs used³. After we adjusted for this sampling error, the estimate of h_C^2 using 7000 SNPs agreed very well with that using all SNPs (**Fig. 1** and **Supplementary Fig. 2**). Moreover, we adjusted the estimate of h_C^2 using all the SNPs on each chromosome for sampling error and found that all the estimates increased by a factor of ~ 1.1 (**Supplementary Fig. 3**).

Modelling the X-linked genetic variance and dosage compensation

The method of estimating the X-linked genetic variance and testing for dosage compensation was described in detail by Yang *et al.*⁴. In brief, under the assumption that the male-female genetic correlation is 1, the X-linked phenotypic covariance between a pair of individuals is⁵

$$\text{cov}_X(y_j^M, y_k^M) = A_{jk}^M \sigma_{X(M)}^2 \text{ for a male-male pair,}$$

$$\text{cov}_X(y_j^F, y_k^F) = A_{jk}^F \sigma_{X(F)}^2 \text{ for a female-female pair and}$$

$$\text{cov}_X(y_j^M, y_k^F) = A_{jk}^{MF} \sigma_{X(M)} \sigma_{X(F)} \text{ for a male-female pair.}$$

where $\sigma_{X(M)}^2$ and $\sigma_{X(F)}^2$ are X-linked genetic variances for males and females, respectively.

If there is no dosage compensation, i.e. each allele has a similar effect on the trait and there are two alleles per locus in females but only one in males, then the X-linked genetic variance for females is twice that for the males, i.e. $\sigma_{X(F)}^2 = 2\sigma_{X(M)}^2$. Under the assumption of full dosage compensation, i.e. each allele in a females has only half the effect of an allele in a male, then the genetic variance on the X-chromosome for females is half that for the males i.e. $\sigma_{X(F)}^2 = \frac{1}{2}\sigma_{X(M)}^2$. The third assumption is that the X-linked genetic variance for males and female are equal i.e. $\sigma_{X(F)}^2 = \sigma_{X(M)}^2$. The X-linked phenotypic covariances under these three assumptions are given in the following table

	No dosage compensation	Full dosage compensation	Equal variance
$\text{cov}_X(y_j^M, y_k^M)$	$\frac{1}{2} A_{jk}^M \sigma_{X(F)}^2$	$2A_{jk}^M \sigma_{X(F)}^2$	$A_{jk}^M \sigma_{X(F)}^2$
$\text{cov}_X(y_j^F, y_k^F)$	$A_{jk}^F \sigma_{X(F)}^2$	$A_{jk}^F \sigma_{X(F)}^2$	$A_{jk}^F \sigma_{X(F)}^2$
$\text{cov}_X(y_j^M, y_k^F)$	$\frac{1}{\sqrt{2}} A_{jk}^{MF} \sigma_{X(F)}^2$	$\sqrt{2} A_{jk}^{MF} \sigma_{X(F)}^2$	$A_{jk}^{MF} \sigma_{X(F)}^2$

If we define d as the lyonization coefficient, then the X-linked covariances can be generalized as

$$\text{cov}_X(y_j^M, y_k^M) = d^2 A_{jk}^M \sigma_{X(F)}^2 \text{ for a male-male pair,}$$

$$\text{cov}_X(y_j^F, y_k^F) = A_{jk}^F \sigma_{X(F)}^2 \text{ for a female-female pair and}$$

$$\text{cov}_X(y_j^M, y_k^F) = d A_{jk}^{MF} \sigma_{X(F)}^2 \text{ for a male-female pair.}$$

where $d = \frac{1}{\sqrt{2}}$ for no dosage compensation, $d = \sqrt{2}$ for full dosage compensation and $d = 1$ for equal X-linked genetic variance for males and females.

Additional models

As both height and BMI have repeated measures in the ARIC cohort and BMI also has repeated measures in the HPFS and NHS cohorts, we fitted a repeatability model for these

repeated records, assuming that the genetic correlation between repeated observations is unity. We estimated the repeatability of height as ~0.99 in the ARIC study and the repeatabilities of weight and BMI of > 0.93 in all cohorts (**Supplementary Table 8**). The estimates of h_G^2 by repeatability model analyses are similar to those using the mean of the repeated measures as in all other analyses (**Table 1 and Supplementary Table 8**). The ratio of an estimate of h_G^2 based upon m repeated records to that of a single observation is $1 / [(1 - \rho) / m + \rho]$ with ρ the repeatability⁶. In this study, $\rho > 0.93$ and m is small, so that our inference based upon the mean of 3 or 4 observations is very similar to that from a single observation.

We fitted a genotype-sex interaction effect in the model, and did not find any significant interaction effect for all the traits (**Supplementary Table 9**). We also estimated the variance explained by all the autosomal SNPs in each gender group in each cohort separately, and did not observe clear evidence of genetic heterogeneity between males and females (**Supplementary Table 10**). However, there are exceptions, for example, the p-value for a test of heterogeneity between males and females for vWF was 0.007 (0.024 after PC-adjustment), which may indicate real genetic difference between males and females for this trait. When taking multiple testing into account, the test was not significant after a Bonferroni correction. For weight and BMI, the p-values only verge on significance even when h_G^2 are estimated to be zero in males, suggesting a lack of power to detect an interaction.

The HPFS and NHS cohorts were ascertained by type-II diabetes (T2D), which might affect the estimate of genetic variance because BMI is a risk factor for T2D⁷. We performed analyses of the variance explained by all the autosomal SNPs separately in T2D cases and controls of the HPFS and NHS cohorts, and did not observe significant differences in estimated genetic variance between cases and controls for all the three traits (**Supplementary**

Table 11). Moreover, we estimated h_G^2 in the combined dataset excluding the T2D cases, and the estimate was not different from that using all samples (**Supplementary Table 12**). These two additional analyses show little, if any, impact of the ascertainment of T2D cases on the estimate of variance explained by the SNPs.

All analyses we have performed are univariate, i.e. a single phenotype at a time. However, multivariate models fit easily in the same analysis framework and the only limitation is computational. As an example, we approximated a full bivariate analysis of height and weight by using logarithms of the phenotypes, exploiting the relationship $\log(\text{BMI}) = \log(\text{Weight}) - 2\log(\text{Height})$, so that from three univariate analyses we can estimate the genetic correlation between $\log(\text{Weight})$ and $\log(\text{Height})$. We estimated a genetic correlation of 0.45 (s.e. = 0.17) between $\log(\text{Weight})$ and $\log(\text{Height})$ (**Supplementary Table 13**). Although this is on the logarithm scale, the estimate on the observed scale is unlikely to be very different. This estimate indicates that for genetic variation tagged by common SNPs there is a substantial overlap in genome-wide additive factors for height and weight.

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