Supplementary Materials: Genomic architecture of human neuroanatomical diversity

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Supplementary Methods

S1. Global test on P-values

We performed our analyses on 12 correlated phenotypes (9 brain regions, plus Height, VIQ and PIQ). Because of these correlations, a standard Bonferroni correction would be too conservative. Indeed, after Bonferroni correction, just a few results would remain statistically significant. However, under the null hypothesis we should expect around 5% of these tests to be significant, but the observed number of P-values <0.05 was much larger. To test the significance of this excess we constructed a statistic S from the list of P-values converted to Z-values obtained for each phenotype:

$$S = \sum_{i=1}^{m} ISF(p_i) \quad ,$$

where *m=12* is the number of tests performed and ISF stands for the inverse survival function of the normal distribution. We then generated the distribution of *S* under the null hypothesis by drawing from a multivariate Gaussian distribution with a variance-covariance structure given by the correlation matrix across phenotypes (Table S1). The significance of the excess of P-values was estimated as the proportion of scores under the null hypothesis that were greater than the observed score. The result of this global test is indicated at the final row of supplementary tables S2, S4-7.

S2. Estimation of statistical power

We used GCTA to simulate 10,000 phenotypes with different heritability values, supported by a different number of causal SNPs. We sampled uniformly heritability values in the range from 0 to 80%, and number of causal SNPs from 1 to 10,000. The causal variants were selected from the non-pruned list of SNPs (~518k SNPs), but the genetic relationship matrices were computed using only SNPs from the pruned set (~270k SNPs). In consequence, the effect of some of the causal variants would be only captured through their linkage disequilibrium with the SNPs retained in the pruned list. Statistical power achieved to detect a given heritability was estimated as the proportion of test with P<0.05 (Figure S3).

S3. Enrichment of variance explained by a SNP set

We used GCTA to partition V_G/V_P among non-overlapping sets of SNPs, for example, genic and nongenic SNPs (2 sets) or SNPs of low, medium and high minor-allele frequency (MAF, 3 sets), etc. We computed a genetic relationship matrix $\mathbf{G_i}$ for each of these *n* sets, and used them as random effects in our model. The variance of our phenotypes $Var(y)$ was therefore decomposed as

$$Var(y)=\sum_{i=1}^{n}\mathbf{G_i}\sigma^2_{gi}+\mathbf{I}\,\sigma^2_e \quad ,$$

where the number of sets would be n=2 for the case of a genic versus nongenic partition, or n=3 in the case of a partition into low, medium and high MAF.

As *a posteriori* analyses, we tested whether the variance explained by one of these sets, genic SNPs for example, was larger than what could be expected given its number of SNPs. The total genetic variance explained is

$$V_T=\sum_{i=1}^{n}V_i \quad ;$$

where N is the total number of SNPs, and N_i the number of SNPs in set i, i=1,...,n. If all SNP sets were equivalent, then the amount of variance they explain should be simply proportional to their length, and then

$$EV_i=\frac{N_i}{N}V_T \quad ,$$

where EV_i is the expected amount of variance explained by the i-th set. We wanted to test whether the difference V_i-EV_i was significantly larger than 0, so we constructed a Z-score

$$Z_i=\frac{V_i-EV_i}{\sqrt{V_{test}}} \quad ,$$

where

$$V_{test}=Var(V_i-EV_i) \quad .$$

Note that V_i here is the estimated explained variance for group i – a random variable; whereas EV_i is a fixed value. We compared the observed value of Z_i with those obtained from >10,000 random permutations, where n non-overlapping SNP sets of N_i SNPs were randomly sampled from all available SNPs (without replacement).

S4. Partition of V_G/V_P based on involvement in central nervous system function

We looked at the proportion of V_G/V_P that could be attributed to genes preferentially expressed in the central nervous system, playing a role in neuronal activity, learning, or involved in synaptic function. We used the set of 2,725 genes defined by Raychaudhuri and collaborators [1] and previously used in the SNP-based heritability analyses of the susceptibility to schizophrenia by Lee and collaborators [2]. We made 3 SNP sets: the 1st set, CNS+, contained all SNPs within ±50 kbp of the 5' and 3' UTR of the gene set (N=61,175, 23% of the total number of SNPs); the 2nd set, CNS-, contained all the remaining genic SNPs (N=113,160, 42% of the total number of SNPs); and the 3rd set regrouped all nongenic SNPs. As before, the genetic-relationship matrices computed using these 3 SNP sets were used in a single linear mixed model. We found that the amount of variance explained by the CNS+ set was not significantly different than what we expected from its number of SNPs (Table S6).

S5. Partition of V_G/V_P based on MAF

Allele frequency variations may provide hints about the evolutionary history of a trait. We estimated the proportion of V_G/V_P that can be attributed to sets of SNPs with low (5-20%), medium (20-35%) and high (35-50%) minor allele frequencies. SNPs in the low-frequency set were the most numerous, 48% of all SNPs, followed by medium-frequency SNPs (30%), and high-frequency alleles (22%). Table S7 shows the result of fitting a linear mixed model with the 3 genetic-relationship matrices computed using the low, medium and high-frequency, in addition to the same fixed effects as previously. We could expect each set to explain a fraction of the variance corresponding to the proportion of the total number of SNPs they represent. Furthermore, because SNPs of high MAF are individually more informative than those with low minor-allele frequency, they could potentially explain more variance (the variance of the genetic-relationship matrices increased from the low to the medium to the high frequency set). However, the amount of variance explained by the different sets was not significantly larger than what we expected from their size.

S6. Correlation between SNP set size and V_G/V_P

We constructed genetic relationship matrices for 3 sets of non-overlapping, randomly selected, SNPs of small, medium and large size. These sets were drawn from all genotyped SNPs, or only from genic SNPs (Ref. Seq.±50kbp), or nongenic SNPs. We ensured that small, medium and large sets contained the same number of SNPs in all 3 groups by selecting 20%, 30% and 50% of the total number of nongenic SNPs, the less numerous group. We performed 100 repetitions of this procedure, each time randomly selecting non-overlapping sets of 20%, 30% and 50% (20%+30%+50%=100%) of SNPs from all genotyped SNPs, or only from the genic or nongenic subgroups. For each repetition, we computed the correlation between V_G/V_P and set size. Correlation coefficients were converted to Z values using Fisher's transformation, and the distribution tested against the null-hypothesis of no correlation (2-tailed t-test). The amount of variance of ICV, BV, subcortical volumes, height, VIQ and PIQ explained by the low, medium and long sets correlated significantly with the size of the SNP set (Fig. S4).

Supplementary Tables

Table S1. Correlation matrix of neuroanatomical phenotypes, height, VIQ and PIQ.

	ICV	BV	Hip	Th	Ca	Pu	Pa	Amy	Acc	Height	VIQ	PIQ
ICV	1	0.96	0.51	0.77	0.52	0.66	0.70	0.28	0.33	0.39	0.18	0.14
BV	0.96	1	0.49	0.76	0.51	0.64	0.67	0.26	0.32	0.34	0.17	0.12
Hip	0.51	0.49	1	0.56	0.39	0.46	0.51	0.33	0.30	0.15	0.17	0.11
Th	0.77	0.76	0.56	1	0.47	0.61	0.70	0.32	0.38	0.29	0.15	0.10
Ca	0.52	0.51	0.39	0.47	1	0.51	0.56	0.21	0.37	0.21	0.09	0.05
Pu	0.66	0.64	0.46	0.61	0.51	1	0.71	0.23	0.39	0.28	0.17	0.11
Pa	0.70	0.67	0.51	0.70	0.56	0.71	1	0.35	0.43	0.33	0.16	0.10
Amy	0.28	0.26	0.33	0.32	0.21	0.23	0.35	1	0.21	0.14	0.10	0.06
Acc	0.33	0.32	0.30	0.38	0.37	0.39	0.43	0.21	1	0.08	0.11	0.12
Height	0.39	0.34	0.15	0.29	0.21	0.28	0.33	0.14	0.08	1	0.06	0.01
VIQ	0.18	0.17	0.17	0.15	0.09	0.17	0.16	0.10	0.11	0.06	1	0.42
PIQ	0.14	0.12	0.11	0.10	0.05	0.11	0.10	0.06	0.12	0.01	0.42	1

Table S2. Estimates of variance explained by genetic factors V_G/V_P (± s.e. %). Effect of removing 10 PC as covariates, and effect of adding Height, VIQ or PIQ as covariates. Statistically significant values in bold (uncorrected). Global test: Global test of excess of significant P-values (per column). Bonferroni: Bonferroni correction of all P-values from the global, per-column, tests. Likelihood ratio test d.f.=1.

	Full model: Age, Sex, Centre and 10 PCs			**Full model excluding 10 PCs**			**Full model plus Height as Covariate**			**Full model plus VIQ as Covariate**			**Full model plus PIQ as Covariate**		
Phenotype	V_G/V_P **(%)**	**LRT**	**P**	V_G/V_P **(%)**	**LRT**	**P**	V_G/V_P **(%)**	**LRT**	**P**	V_G/V_P **(%)**	**LRT**	**P**	V_G/V_P **(%)**	**LRT**	**P**
ICV	**54±23**	**5.3**	**0.0106**	**56±23**	**6.07**	**0.0069**	**59±24**	**5.42**	**0.0010**	32±24	1.63	0.1010	**49 ± 24**	**3.91**	**0.0241**
BV	**44±23**	**3.48**	**0.0309**	**50±23**	**4.84**	**0.0139**	**46±24**	**3.33**	**0.0341**	25±25	1.01	0.1580	38 ± 24	2.34	0.0630
Hip	**53±23**	**5.4**	**0.0101**	**51±22**	**5.47**	**0.0097**	**64±24**	**6.88**	**0.0044**	**53±24**	**4.44**	**0.0176**	**56 ± 24**	**5.17**	**0.0115**
Th	22±24	0.84	0.1790	30±23	1.65	0.0993	24±24	0.88	0.1740	13±25	0.29	0.2960	22 ± 25	0.76	0.1920
Ca	16±23	0.46	0.2500	15±23	0.42	0.2580	37±24	2.18	0.0697	8±24	0.12	0.3640	14 ± 24	0.32	0.2860
Pa	31±23	1.7	0.0968	27±23	1.33	0.1250	29±24	1.40	0.118	32±25	1.56	0.1060	40 ± 25	2.44	0.0593
Pu	**54±23**	**5.48**	**0.0096**	**48±23**	**4.41**	**0.0178**	**64±24**	**6.84**	**0.0045**	**51±24**	**4.11**	**0.0213**	**58 ± 24**	**5.58**	**0.0091**
Amy	**45±23**	**3.54**	**0.0301**	**42±23**	**3.20**	**0.0368**	**44±24**	**2.97**	**0.0425**	**51±25**	**3.83**	**0.0251**	**53 ± 25**	**4.20**	**0.0202**
Acc	**52±23**	**4.92**	**0.0133**	**47±23**	**4.12**	**0.0211**	**53±24**	**4.72**	**0.0149**	**57±24**	**5.32**	**0.0105**	**56 ± 24**	**5.11**	**0.0119**
Height	**56±23**	**6.08**	**0.0069**	**55±23**	**6.04**	**0.0070**	–	–	–	**52±24**	**4.80**	**0.0142**	**55 ± 24**	**5.47**	**0.0097**
VIQ	**56±25**	**4.98**	**0.0128**	**66±24**	**7.99**	**0.0024**	**51±25**	**4.02**	**0.0225**	–	–	–	**41 ± 24**	**2.74**	**0.0490**
PIQ	**52±25**	**4.18**	**0.0204**	**56±24**	**5.73**	**0.0084**	**45±25**	**3.14**	**0.0381**	36±24	2.05	0.0761	–	–	–
Global Test (Bonferroni)			**0.0011 (0.0057)**			**0.0009 (0.0044)**			**0.0016 (0.0078)**			**0.0115 (0.0576)**			**0.0038 (0.0189)**

Table S3. Genetic correlation between phenotypes. Values under the diagonal are genetic correlations (± s.e., %), over the diagonal, likelihood ratio test (P-value). Significant (uncorrected) values in bold.

	ICV	BV	Hip	Th	Ca	Pa	Pu	Amy	Acc	Height	VIQ	PIQ
ICV		NA	**6.31(.006)**	.77(.19)	.20(.33)	1.18(.14)	1.93(.08)	1.34(.12)	.79(.19)	.43(.25)	**6.74(.004)**	.0(.48)
BV	.96±.04		.0(.5)	.86(.18)	.0(.48)	1.15(.14)	.96(.16)	1.86(.09)	.3(.29)	.48(.24)	**4.8(.01)**	.0(.48)
Hip	**1.00±.25**	1.00±.34		.0(.5)	2.0(.08)	–	2.28(.07)	**2.83(.05)**	1.38(.12)	2.52(.06)	**2.57(.05)**	.79(.19)
Th	.54±.31	.62±.31	1.00±.45		.01(.46)	1.32(.13)	.03(.44)	.69(.20)	1.33(.12)	.65(.21)	1.55(.11)	.10(.38)
Ca	.28±.49	.04±.68	.82±.57	-.10±1.06		.01(.46)	.14(.36)	.0(.49)	.28(.30)	.14(.35)	2.07(.08)	.01(.46)
Pa	.51±.28	.55±.32	–	.87±.33	.07±0.81		1.85(.09)	1.11(.15)	1.75(.09)	**5.03(0.01)**	**4.53(0.02)**	.08(.39)
Pu	.48±.23	.37±.28	.49±.25	.09±.50	.23±0.51	.66±.23		.42(.26)	**2.67(.05)**	**6.36(.006)**	**2.84(.05)**	.04(.43)
Amy	.41±.30	.53±.34	**.59±.28**	.47±.47	.02±0.64	.50±.38	.22±.32		.01(.47)	.48(.24)	.15(.35)	.57(.23)
Acc	.30±.28	.21±.33	.38±.28	.61±.37	.34±0.50	.60±.32	**.54±.24**	-.03±0.37		.07(.39)	**3.55(.03)**	1.42(.12)
Height	.20±.29	.23±.32	.43±.28	.36±.43	.14±0.37	**.79±35**	**.67±.28**	.24±0.34	.08±.31		**3.41(.03)**	.58(.22)
VIQ	**.95±.41**	**.89±.47**	**.52±.32**	.72±.70	1.00±1.08	**.85±.4**6	**.55±.33**	.13±0.33	**.59±.34**	**.59±.35**		3.58(.03)
PIQ	.02±.37	.02±.42	.29±.31	-.19±.64	.07±0.65	.11±.39	.06±.32	-.28±0.39	.38±.32	.26±.36	**.69±.25**	

Table S4. Estimates of variance explained (±s.e. %) by genic subsets of genotyped markers, including neighbouring regulatory regions within 0, ±20 and ±50 Kbp. Statistically significant values in bold (uncorrected). Global test: Global test of excess of significant P-values.

Genic regions = Ref. Seq.±0Kbp

Phenotype	LRT (df=2)	P_{model}	V_{genic}/V_P (%)	V_{genic}/V_G (%)	$V_{nongenic}/V_P$ (%)	P_{genic}	$P_{nongenic}$
ICV	5.42	**0.0333**	26±16	48	28±20	0.0536	0.0928
BV	3.5	0.0869	19±16	43	25±20	0.1190	0.1160
Hip	5.44	**0.0329**	19±16	36	**34±20**	0.1130	0.0448
Th	0.86	0.3253	10±16	45	12±20	0.2610	0.2730
Ca	0.98	0.3063	0±16	0	19±20	0.5000	0.1620
Pa	2.54	0.1404	25±16	81	4±20	0.0665	0.4210
Pu	6.46	**0.0198**	9±16	17	**46±19**	0.2840	0.0094
Amy	4.14	0.0631	7±17	16	**38±20**	0.3420	0.0305
Acc	7.54	**0.0115**	0±17	0	**53±20**	0.5000	0.0034
Height	6.66	**0.0179**	12±17	21	**46±21**	0.2490	0.0132
VIQ	**8.92**	**0.0058**	**51±17**	91	2±21	0.0018	0.4580
PIQ	4.4	0.0554	28±17	54	25±21	0.0578	0.1130
Global Test		**0.0026**					

Genic regions = Ref. Seq.±20Kbp

Phenotype	LRT (df=2)	P_{model}	V_{genic}/V_P (%)	V_{genic}/V_G (%)	$V_{nongenic}/V_P$ (%)	P_{genic}	$P_{nongenic}$
ICV	6.78	**0.0169**	**45±18**	83	8±17	0.0065	0.3260
BV	4.06	0.0657	**34±18**	77	10±17	0.0317	0.2880
Hip	5.6	**0.0304**	23±17	43	**30±17**	0.0814	0.0402
Th	1.06	0.2943	18±18	82	4±17	0.1590	0.3940
Ca	0.52	0.3855	12±18	75	4±17	0.2550	0.4150
Pa	2.32	0.1567	27±18	87	3±17	0.0691	0.4390
Pu	5.66	**0.0295**	24±18	44	**30±17**	0.0800	0.0357
Amy	6.98	**0.0153**	0±18	0	**46±17**	0.5000	0.0044
Acc	5	**0.0410**	24±18	46	27±17	0.0977	0.0545
Height	6.2	**0.0225**	25±19	45	**31±18**	0.0849	0.0414
VIQ	9.56	**0.0042**	**56±19**	100	0±18	0.0010	0.5000
PIQ	5.1	**0.0390**	41±19	79	11±18	0.0167	0.2760
Global Test		**0.0084**					

Genic regions = Ref. Seq.±50Kbp

Phenotype	LRT (df=2)	P_{model}	V_{genic}/V_P (%)	V_{genic}/V_G (%)	$V_{nongenic}/V_P$ (%)	P_{genic}	$P_{nongenic}$
ICV	6.64	**0.0181**	**49±19**	91	4±15	0.0058	0.3940
BV	4.98	**0.0415**	**43±19**	98	0±15	0.0131	0.4980
Hip	5.94	**0.0257**	27±18	51	**28±15**	0.0638	0.0332
Th	1.64	0.2202	23±19	105	0±15	0.1000	0.5000
Ca	0.82	0.3318	17±19	106	0±15	0.1820	0.5000
Pa	2.8	0.1233	**30±19**	97	0±15	0.0473	0.5000
Pu	5.48	**0.0323**	**35±19**	65	19±15	0.0297	0.0955
Amy	7.12	**0.0142**	6±19	13	**39±15**	0.3830	0.0043
Acc	4.94	**0.0423**	31±19	60	20±15	0.0528	0.0848
Height	6.5	**0.0194**	28±20	50	**29±16**	0.0775	0.0344
VIQ	6.78	**0.0169**	**53±20**	95	1±16	0.0047	0.4720
PIQ	4.6	**0.0501**	**42±20**	81	10±16	0.0213	0.2640
Global Test		**0.0067**					

Table S5. Enrichment of variance explained by genic SNPs compared with their number. Genic SNPs are those within Ref. Seq. boundaries ±50kbp. P-values were obtained through 10,036 random permutations. Statistically significant values in bold (uncorrected). Global test: Global test of excess of significant P-values.

Phenotype	V_{genic} (%)	$V_{expected}$ (%)	V_{test} (%)	P(V_{genic}>$V_{expected}$)
ICV	49	34	23	**0.0139**
BV	43	28	28	**0.0007**
Hip	27	34	22	0.7655
Th	23	14	51	**0.0229**
Ca	17	10	74	0.0707
Pa	30	20	40	**0.0102**
Pu	35	34	22	0.5094
Amy	6	29	27	0.9976
Acc	31	33	24	0.5762
Height	28	36	23	0.7489
VIQ	53	36	24	**0.0008**
PIQ	42	33	25	0.2579
Global Test				**0.0073**

Table S6. Variance partition by CNS implication. Statistically significant values in bold (uncorrected). Global test: Global test of excess of significant P-values.

Phenotype	LRT (df=3)	P_{model}	V_{CNS+}/V_P (%)	V_{CNS-}/V_P (%)	$V_{nongenic}/V_P$ (%)	P_{CNS+}	P_{CNS-}	$P_{nongenic}$
ICV	6.78	**0.0396**	15±12	**43±18**	4±15	0.1100	0.0075	0.3940
BV	5.24	0.0775	15±12	**36±18**	0±15	0.1070	0.0192	0.5000
Hip	6.44	**0.0460**	14±12	14±17	**28±15**	0.1160	0.2040	0.0347
Th	2.12	0.2739	0±12	**32±17**	0±15	0.5000	0.0233	0.5000
Ca	2.38	0.2487	0±12	22±18	0±15	0.5000	—	0.5000
Pa	2.78	0.2134	4±12	**33±18**	0±15	0.3310	0.0247	0.5000
Pu	5.94	0.0573	0±12	**41±17**	18±15	0.5000	0.0083	0.1050
Amy	7.38	**0.0304**	0±12	7±18	**38±15**	0.5000	0.3450	0.0041
Acc	4.94	0.0881	8±12	21±18	21±15	0.2540	0.1220	0.0841
Height	7.36	**0.0306**	0±13	**31±19**	**28±16**	0.5000	0.0390	0.0301
VIQ	6.94	**0.0369**	17±13	**37±19**	2±16	0.0931	0.0247	0.4630
PIQ	4.96	0.0874	4±13	30±19	10±16	0.3710	0.0621	0.2620
Global Test		**0.0210**						

Table S7. Variance partition by Minor Allele Frequency (MAF) set. P_{model}: Significance of the complete model. $P_{5\text{-}20}$, $P_{20\text{-}35}$, $P_{35\text{-}50}$: Significance of the variance estimation per MAF range. Statistically significant values in bold (uncorrected). Global test: Global test of excess of significant P-values.

Phenotype	LRT (df=3)	P_{model}	$V_{5\text{-}20}/V_P$ (%)	$V_{20\text{-}35}/V_P$ (%)	$V_{35\text{-}50}/V_P$ (%)	$P_{5\text{-}20}$	$P_{20\text{-}35}$	$P_{35\text{-}50}$
ICV	7.4	**0.0301**	44±21	0±19	15±15	0.0139	0.5000	0.1450
BV	5.44	0.0711	**37±21**	0±19	12±15	0.0285	0.5000	0.1810
Hip	8.28	**0.0203**	**45±21**	16±18	0±16	0.0146	0.1960	0.5000
Th	1.66	0.3229	0±22	19±19	3±16	0.5000	0.1510	0.3890
Ca	1.02	0.3982	0±22	14±18	1±15	0.5000	0.2100	0.4310
Pa	2.7	0.2201	9±22	25±19	0±15	0.3320	0.0843	0.5000
Pu	9.8	**0.0102**	0±21	**48±19**	6±16	0.5000	0.0043	0.3270
Amy	4.12	0.1244	10±22	26±18	6±15	0.3240	0.0727	0.3520
Acc	6.56	**0.0437**	27±22	0±18	**27±16**	0.1030	0.5000	0.0359
Height	7.96	**0.0234**	1±22	**37±20**	16±17	0.4820	0.0329	0.1730
VIQ	5.18	0.0795	21±23	16±20	19±17	0.1770	0.2140	0.1290
PIQ	6.22	0.0507	0±23	22±20	28±17	0.5000	0.1310	0.0486
Global Test		**0.0163**						

Table S8. Comparison of VG/VP and heritability estimations from recent twin studies (Kremen et al 2010, Yoon et al 2011, den Braber et al 2013).

	ICV	BV	Hip	Th	Ca	Pa	Pu	Amy	Acc
VG/VP	54±23	44±23	53±23	22±24	16±23	31±23	54±23	45±23	52±23
den Braber et al, mean h2(95% CI)			76 (66-83)	81 (74-85)	87 (82-91)	70 (56-80)	85 (80-89)	67 (57-76)	67 (56-75)
Kremen et al, mean h2(95% CI)	79 (52-87)		64 (36-74)	64 (35-81)	75 (43-91)	71 (33-81)	85 (56-90)	65 (28-74)	54 (14-70)
Yoon et al, mean h2(95% CI)		70 (34-81)		53 (1-80)	38 (0-74)	79 (39-88)	78 (52-86)		

Supplementary Figures

Figure S1. Volume distribution of the neuroanatomical endophenotypes analysed. All volumes show a similar variability (the larger variability of the nucleus accumbens and amygdala may be related to their small size, which makes their segmentation more difficult). **ICV**: intracranial volume, **BV**: total brain volume, **Hip**: hippocampus, **Th**: thalamus, **Ca**: caudate nucleus, **Pu**: putamen, **Pa**: globus pallidus, **Amy**: amygdala, **Acc**: nucleus accumbens.

Figure S2. Population structure. The IMAGEN cohort has a strong European-ethnicity component. **a.** Principal component analysis of the IBS matrix of the Imagen cohort combined with HapMap 3. Top figure: Plot of the 1st and 2nd principal components. **ASW**: African ancestry in Southwest USA, **CEU**: Utah residents with Northern and Western European ancestry from the CEPH collection, **CHB**: Han Chinese in Beijing – China, **CHD**: Chinese in Metropolitan Denver – Colorado, **GIH**: Gujarati Indians in Houston – Texas, **JPT**: Japanese in Tokyo – Japan, **LWK**: Luhya in Webuye – Kenya, **MEX**: Mexican ancestry in Los Angeles – California, **MKK**: Maasai in Kinyawa – Kenya, **TSI**: Toscani in Italia, **YRI**: Yoruba in Ibadan – Nigeria. Bottom-figure: 1st and 3rd principal components. 99% confidence ellipsoid of the Imagen cohort drawn in black. **b.** Ethnic composition of the Imagen cohort based in 4 groups, likely corresponding to European (blue), Indian (red), Asian (green) and African (magenta) components. Top figure: Imagen cohort. Bottom figure: HapMap 3 cohort.

Figure S3. Statistical power as a function of heritability. Estimation of statistical power obtained through simulation of 10,000 phenotypes with different heritability values, supported by a different number of causal SNPs. We had >50% statistical power to find heritability values >45%, and >70% statistical power to find heritability values >55%.

Figure S4. V_G/V_P versus gene set length. The amount of variance captured by SNPs increased with the number of SNPs used to compute genetic-relationship matrices (Supplementary Methods S6). In most cases, this was only the case for genic SNPs (Ref.Seq.±50kpb). * P<0.01, ** P<0.001, *** P<0.0001, uncorrected.