Evidence of widespread selection on standing variation in Europe at height-associated SNPs – Supplemental Material

Michael C. Turchin.[1,2,3,4,5*], Charleston W.K. Chiang [1,2,3,4,5,6*], Cameron D. Palmer [1,2,3,4,5], Sriram Sankararaman [5,6], David Reich [5,6], GIANT consortium[7], Joel N. Hirschhorn [1,2,3,4,5,6]

[1]Division of Genetics, Children's Hospital Boston, Boston, MA 02115
[2]Division of Endocrinology, Children's Hospital Boston, Boston, MA 02115
[3]Program in Genomics, Children's Hospital Boston, Boston, MA 02115
[4]Metabolism Initiative, Broad Institute, Cambridge, MA 02141
[5]Program in Medical and Population Genetics, Broad Institute, Cambridge, MA 02141
[6]Department of Genetics, Harvard Medical School, Boston, MA 02115
[7]For a full list of contributing members and institutions, please see Supplementary Note
[*] These authors contributed equally to this work
To whom correspondence should be addressed: joelh@broadinstitute.org

Supplementary Tables

Supplementary Table 1. Survey of mean height across different European populations as reported in literature

Country	Year	Age Range	N (x1000)	Male Height (cm)	Female Height (cm)	Reference
Denmark	2002	20-40	NA	181.7	168.2	Ref 1
Denmark	2004	18	NA	181	NA	Ref 2
Netherlands	1992	18	NA	181	NA	Ref 2
Norway	1992-1998	NA	NA	181	167.3	Ref 1
Sweden	2003	18	NA	180	NA	Ref 2
Sweden	1990-1997	18	337.2	179.9	NA	Ref 3
Finland	2000-2002	21-27	NA	179.5	166.3	Ref 1
Netherlands	1991-1992	20-74	10.2	178.7	167.1	Ref 4
Norway	2004	18	NA	179	NA	Ref 2
Norway	1992-1994	20-74	5	178.9	165.8	Ref 4
Belgium	1992	18	NA	178	NA	Ref 2
Sweden	1991	20-74	4.9	177.9	164.6	Ref 4
Denmark	1986-1987	20-74	4	177.1	165.2	Ref 4
Sweden	1973	15-47	NA	177.2	164.6	Ref 1
Italy	2003	20	NA	178	163.4	Ref 1
UK	2008	25-34	2.22	177.6	163.7	Ref 5
Finland	1990-1991	20-74	6.7	176.6	163.5	Ref 4
UK	1994-2001	20-40	NA	NA	163.7	Ref 1
UK	2000	25-34	1.37	176.9	162.9	Ref 5

UK	1993	25-34	3.17	176.4	163	Ref 5
Switzerland	1992-1993	20-74	13.3	175.4	164	Ref 4
Germany	1988-1991	20-74	10.6	175.4	162.8	Ref 4
Spain	1995	18	NA	175	NA	Ref 2
Italy	1996	18	NA	174	NA	Ref 2
France	1991	20-74	13.4	173.1	161.8	Ref 4
Italy	1990-1991	20-74	37	172.2	162.1	Ref 4
Portugal	1999	18	NA	173	NA	Ref 2
Spain	1987	20-74	24.9	170	160.3	Ref 4

Mean height, stratified by gender, were extracted from the literature cited. The studies were roughly sorted in decreasing order of the average height. Because of the different methods and time points by which these measurements were taken, this table is meant to represent general qualitative trends across Europe rather than exact values per country. For entries from Ref 1, dizygotic twin data were used. For entries from Ref 2, the numbers were estimated from their figure 1. NA, not available.

Supplementary Table 2. Sign Test and Mean NEur – SEur AF difference for POPRES, and for MIGen using SEur AF-adjusted p-values

POPRES		**SEur AF-adjusted p-values**	
Sign Test (N > S)	p-value	Sign Test (N > S)	p-value
70 out of 109	0.0039	111 out of 185	0.0080
Mean NEur-SEur AF	p-value	Mean NEur-SEur AF	p-value
0.017	7.1E-04	0.011	7.0E-04

Sign tests and mean NEur – SEur AF difference tests were calculated as described in the Materials and Methods for the independent dataset POPRES (left columns; UK as Northern European and Italy as Southern European), and for MIGen with height SNPs ascertained from GIANT data using SEur AF-adjusted p-values as described in Materials and Methods (right columns). NEur, Northern European. SEur, Southern European. AF, allele frequency.

Supplementary Table 3. Likelihood ratio test and maximum likelihood estimate of s for forward simulated genetic drift data

Supplementary Table 3A – Top ~1,400 SNPs

Input N_e	Input s	Estimated s	NEur - SEur AF	LRT Statistic	LRT p-value
10000	0.076	0.078	0.0050	27.69	1.42E-07
20000	0.076	0.075	0.0047	25.83	3.72E-07
10000	0.038	0.039	0.0047	28.00	1.21E-07
20000	0.038	0.032	0.0055	35.72	2.27E-09
20000	0.019	0.020	0.0049	26.70	2.37E-07
50000	0.0076	0.0080	0.0052	33.23	8.17E-09

Supplementary Table 3B – Genome-wide data

Input N_e	Input s	Estimated s	NEur - SEur AF	LRT Statistic	LRT p-value
10000	0.076	0.077	0.0017	212.85	3.28E-48
20000	0.076	0.074	0.0011	131.61	1.83E-30
10000	0.038	0.037	0.0013	134.56	4.12E-31
20000	0.038	0.041	0.0017	199.39	2.84E-45
20000	0.019	0.019	0.0012	142.31	8.32E-33
50000	0.0076	0.0081	0.0017	235.79	3.25E-53

LRT results for forward genetic drift simulations given different combinations of input parameters s (the actual selective coefficient is $w = s*\beta$, where β is the estimated effect size on height) and N_e (the effective population size). Supplementary Table 3A shows analysis using only the top ~1,400 SNPs of the simulated data, and Supplementary Table 3B shows analysis using the entire simulated genome-wide data set of ~56,000 SNPs. See Supplementary Methods section 3.5 for additional details of the simulations. The results for the median of 5 replicate simulations are shown for each combination of input parameters. Input s values (0.076, 0.038, 0.019, and 0.0076) correspond to the values we estimated in the actual data where T (number of generations) equals 50, 100, 200 and 500, respectively. NEur, Northern European. SEur, Southern European. AF, allele frequency.

Supplementary Table 4. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in the top ~1,400 SNPs using the MIGen dataset (U.S. individuals of Northern European ancestry vs. Spanish individuals)

T (gener-ations)	s (w=sβ)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	2.4E-03	1.4E-01	66.79	3.02E-16	65.24	6.63E-16	-1.546	0.21
50	9.5E-04	5.6E-02	66.80	3.00E-16	65.25	6.59E-16	-1.549	0.21
100	4.7E-04	2.8E-02	66.80	3.01E-16	65.25	6.58E-16	-1.545	0.21
200	2.4E-04	1.4E-02	66.80	3.01E-16	65.26	6.58E-16	-1.541	0.21
400	1.2E-04	7.0E-03	66.80	3.01E-16	65.26	6.57E-16	-1.541	0.21
600	8.0E-05	4.6E-03	66.80	3.01E-16	65.26	6.57E-16	-1.541	0.21
800	6.0E-05	3.5E-03	66.80	3.01E-16	65.26	6.57E-16	-1.541	0.21
1000	5.0E-05	2.8E-03	66.61	3.31E-16	65.26	6.57E-16	-1.352	0.24
1200	4.0E-05	2.3E-03	66.80	3.01E-16	65.26	6.57E-16	-1.541	0.21
1400	3.0E-05	2.0E-03	65.94	4.65E-16	65.26	6.57E-16	-0.681	0.41
1600	3.0E-05	1.7E-03	66.80	3.01E-16	65.26	6.57E-16	-1.541	0.21
1800	3.0E-05	1.5E-03	65.52	5.76E-16	65.26	6.57E-16	-0.261	0.61
2000	2.0E-05	1.4E-03	65.18	6.85E-16	65.26	6.57E-16	0.081	0.78

Analyses were carried out as described in Table 1, but now presented are results using a different model of selection, w = s (where selection was constant for each variant across the entire genome). Likelihood ratio test (LRT) statistics and p-values are included for w = s vs. drift and w = s*β vs. w = s, as well as the previous models from Table 1. Northern- and Southern-European allele frequencies are estimated from the MIGen Harps (NEur) and Regicor (SEur) datasets. For computational efficiency, these and all other LRT results presented in the Supplemental Material, use a linear approximation to estimate the allele frequency differences (see Supplemental Methods, section 2.5; compare to results in Table 1). Note that our analysis in this and the following Supplementary Tables is actually estimating the product of T and s. Because our estimates of T and s cannot be decoupled, the LRT statistics and p values are nearly identical across ranges of T; accordingly, we are not estimating T but are instead estimating s under a range of values for T that are likely to span the actual (unknown) value of T.

Supplementary Table 5. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in the top ~1,400 SNPs using the MIGen dataset (Swedish individuals vs. Spanish individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	2.8E-03	1.8E-01	23.91	1.01E-06	29.80	4.80E-08	5.89	0.015
50	1.1E-03	7.4E-02	23.91	1.01E-06	29.81	4.76E-08	5.90	0.015
100	5.5E-04	3.7E-02	23.91	1.01E-06	29.82	4.74E-08	5.91	0.015
200	2.8E-04	1.8E-02	23.91	1.01E-06	29.82	4.74E-08	5.91	0.015
400	1.4E-04	9.2E-03	23.91	1.01E-06	29.82	4.73E-08	5.91	0.015
600	9.0E-05	6.1E-03	23.91	1.01E-06	29.82	4.73E-08	5.92	0.015
800	7.0E-05	4.6E-03	23.91	1.01E-06	29.82	4.73E-08	5.92	0.015
1000	6.0E-05	3.7E-03	23.72	1.11E-06	29.82	4.73E-08	6.10	0.014
1200	5.0E-05	3.1E-03	23.72	1.11E-06	29.82	4.73E-08	6.10	0.014
1400	4.0E-05	2.6E-03	23.91	1.01E-06	29.82	4.73E-08	5.92	0.015
1600	3.0E-05	2.3E-03	23.52	1.24E-06	29.82	4.73E-08	6.30	0.012
1800	3.0E-05	2.0E-03	23.91	1.01E-06	29.82	4.73E-08	5.92	0.015
2000	3.0E-05	1.8E-03	23.72	1.11E-06	29.82	4.73E-08	6.10	0.014

Analyses were carried out as described in Supplementary Table 4, but using individuals from Sweden (Malmo) and Spain (Regicor) from the MIGen dataset to estimate Northern- and Southern-European allele frequencies.

Supplementary Table 6. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in the top ~1,400 SNPs using the POPRES dataset (UK individuals vs. Italian individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	4.6E-03	2.7E-01	169.68	8.70E-39	155.73	9.72E-36	-13.95	1.88E-04
50	1.9E-03	1.1E-01	169.77	8.30E-39	155.68	9.96E-36	-14.10	1.74E-04
100	9.2E-04	5.3E-02	169.80	8.18E-39	155.66	1.00E-35	-14.14	1.70E-04
200	4.6E-04	2.7E-02	169.82	8.12E-39	155.65	1.01E-35	-14.17	1.67E-04
400	2.3E-04	1.3E-02	169.82	8.08E-39	155.64	1.01E-35	-14.18	1.66E-04
600	1.5E-04	8.8E-03	169.72	8.54E-39	155.64	1.01E-35	-14.07	1.76E-04
800	1.2E-04	6.6E-03	169.57	9.17E-39	155.64	1.01E-35	-13.93	1.90E-04
1000	9.0E-05	5.3E-03	169.72	8.53E-39	155.64	1.01E-35	-14.07	1.76E-04
1200	8.0E-05	4.4E-03	169.58	9.16E-39	155.64	1.01E-35	-13.93	1.90E-04
1400	7.0E-05	3.8E-03	169.21	1.10E-38	155.64	1.01E-35	-13.57	2.30E-04
1600	6.0E-05	3.3E-03	169.58	9.16E-39	155.64	1.01E-35	-13.93	1.89E-04
1800	5.0E-05	2.9E-03	169.72	8.52E-39	155.64	1.01E-35	-14.08	1.75E-04
2000	5.0E-05	2.7E-03	168.68	1.43E-38	155.64	1.01E-35	-13.04	3.05E-04

Analyses were carried out as described in Supplementary Table 4, but using individuals from the UK and Italy from the POPRES dataset to estimate Northern- and Southern-European allele frequencies.

Supplementary Table 7. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in the top ~1,400 SNPs using the POPRES dataset (UK individuals vs. Portugal individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	3.5E-03	2.1E-01	76.18	2.59E-18	76.21	2.55E-18	0.029	0.86
50	1.4E-03	8.4E-02	76.21	2.55E-18	76.24	2.52E-18	0.027	0.87
100	7.0E-04	4.2E-02	76.22	2.54E-18	76.24	2.51E-18	0.026	0.87
200	3.5E-04	2.1E-02	76.22	2.54E-18	76.25	2.50E-18	0.026	0.87
400	1.7E-04	1.1E-02	76.18	2.59E-18	76.25	2.50E-18	0.068	0.79
600	1.2E-04	7.0E-03	76.14	2.64E-18	76.25	2.50E-18	0.11	0.74
800	9.0E-05	5.2E-03	76.14	2.64E-18	76.25	2.50E-18	0.11	0.74
1000	7.0E-05	4.2E-03	76.22	2.53E-18	76.25	2.50E-18	0.025	0.87
1200	6.0E-05	3.5E-03	76.14	2.64E-18	76.25	2.50E-18	0.11	0.74
1400	5.0E-05	3.0E-03	76.22	2.53E-18	76.25	2.50E-18	0.025	0.87
1600	4.0E-05	2.6E-03	75.72	3.27E-18	76.25	2.50E-18	0.53	0.47
1800	4.0E-05	2.3E-03	76.14	2.64E-18	76.25	2.50E-18	0.11	0.74
2000	3.0E-05	2.1E-03	74.75	5.33E-18	76.25	2.50E-18	1.50	0.22

Analyses were carried out as described in Supplementary Table 4, but using individuals from the UK and Portugal from the POPRES dataset to estimate Northern- and Southern-European allele frequencies.

Supplementary Table 8. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in the top ~1,400 SNPs using the POPRES dataset (UK individuals vs. Swiss-French individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	1.3E-03	7.6E-02	20.03	7.61E-06	18.88	1.39E-05	-1.16	0.28
50	5.2E-04	3.1E-02	20.04	7.60E-06	18.88	1.39E-05	-1.16	0.28
100	2.6E-04	1.5E-02	20.04	7.59E-06	18.88	1.39E-05	-1.16	0.28
200	1.3E-04	7.6E-03	20.04	7.59E-06	18.88	1.39E-05	-1.16	0.28
400	7.0E-05	3.8E-03	19.94	8.01E-06	18.88	1.39E-05	-1.06	0.30
600	4.0E-05	2.5E-03	19.91	8.14E-06	18.88	1.39E-05	-1.03	0.31
800	3.0E-05	1.9E-03	19.91	8.14E-06	18.88	1.39E-05	-1.03	0.31
1000	3.0E-05	1.5E-03	19.60	9.55E-06	18.88	1.39E-05	-0.72	0.40
1200	2.0E-05	1.3E-03	19.91	8.14E-06	18.88	1.39E-05	-1.03	0.31
1400	2.0E-05	1.1E-03	19.94	8.00E-06	18.88	1.39E-05	-1.06	0.30
1600	2.0E-05	9.5E-04	19.03	1.29E-05	18.88	1.39E-05	-0.15	0.70
1800	1.0E-05	8.5E-04	18.10	2.10E-05	18.88	1.39E-05	0.78	0.38
2000	1.0E-05	7.6E-04	18.94	1.35E-05	18.88	1.39E-05	-0.06	0.81

Analyses were carried out as described in Supplementary Table 4, but using individuals from the UK and Switzerland (French) from the POPRES dataset to estimate Northern- and Central-European allele frequencies.

Supplementary Table 9. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in the top ~1,400 SNPs using the POPRES dataset (Swiss-French individuals vs. Italian individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	3.3E-03	1.9E-01	105.46	9.66E-25	96.23	1.02E-22	-9.23	0.0024
50	1.3E-03	7.5E-02	105.50	9.47E-25	96.20	1.04E-22	-9.31	0.0023
100	6.6E-04	3.8E-02	105.51	9.43E-25	96.19	1.04E-22	-9.32	0.0023
200	3.3E-04	1.9E-02	105.52	9.40E-25	96.18	1.05E-22	-9.34	0.0022
400	1.6E-04	9.4E-03	105.47	9.61E-25	96.18	1.05E-22	-9.29	0.0023
600	1.1E-04	6.2E-03	105.52	9.38E-25	96.18	1.05E-22	-9.34	0.0022
800	8.0E-05	4.7E-03	105.48	9.60E-25	96.18	1.05E-22	-9.30	0.0023
1000	7.0E-05	3.7E-03	105.03	1.20E-24	96.18	1.05E-22	-8.85	0.0029
1200	5.0E-05	3.1E-03	104.79	1.36E-24	96.18	1.05E-22	-8.61	0.0033
1400	5.0E-05	2.7E-03	105.03	1.20E-24	96.18	1.05E-22	-8.85	0.0029
1600	4.0E-05	2.3E-03	105.48	9.60E-25	96.18	1.05E-22	-9.30	0.0023
1800	4.0E-05	2.1E-03	104.48	1.59E-24	96.18	1.05E-22	-8.31	0.0040
2000	3.0E-05	1.9E-03	104.79	1.36E-24	96.18	1.05E-22	-8.62	0.0033

Analyses were carried out as described in Supplementary Table 4, but using individuals from Switzerland (French) and Italy from the POPRES dataset to estimate Central- and Southern-European allele frequencies.

Supplementary Table 10. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in the top ~1,400 SNPs using the POPRES dataset (Swiss-French individuals vs. Portugal individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	2.4E-03	1.4E-01	38.79	4.72E-10	37.48	9.21E-10	-1.31	0.25
50	9.5E-04	5.6E-02	38.80	4.70E-10	37.48	9.21E-10	-1.32	0.25
100	4.7E-04	2.8E-02	38.80	4.69E-10	37.48	9.21E-10	-1.32	0.25
200	2.4E-04	1.4E-02	38.80	4.70E-10	37.48	9.22E-10	-1.31	0.25
400	1.2E-04	7.0E-03	38.80	4.70E-10	37.48	9.21E-10	-1.31	0.25
600	8.0E-05	4.7E-03	38.80	4.70E-10	37.48	9.22E-10	-1.31	0.25
800	6.0E-05	3.5E-03	38.80	4.70E-10	37.48	9.22E-10	-1.31	0.25
1000	5.0E-05	2.8E-03	38.68	5.00E-10	37.48	9.22E-10	-1.19	0.27
1200	4.0E-05	2.3E-03	38.80	4.70E-10	37.48	9.22E-10	-1.31	0.25
1400	3.0E-05	2.0E-03	38.32	6.00E-10	37.48	9.22E-10	-0.84	0.36
1600	3.0E-05	1.7E-03	38.80	4.70E-10	37.48	9.22E-10	-1.31	0.25
1800	3.0E-05	1.6E-03	38.02	6.99E-10	37.48	9.22E-10	-0.54	0.46
2000	2.0E-05	1.4E-03	37.89	7.50E-10	37.48	9.22E-10	-0.40	0.53

Analyses were carried out as described in Supplementary Table 4, but using individuals from Switzerland (French) and Portugal from the POPRES dataset to estimate Central- and Southern-European allele frequencies.

Supplementary Table 11. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in genome-wide data using the MIGen dataset (U.S. individuals of Northern European ancestry vs. Spanish individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	9.7E-04	1.9E-01	428.47	3.50E-95	666.49	5.79E-147	238.02	1.06E-53
50	3.9E-04	7.6E-02	428.63	3.24E-95	666.91	4.70E-147	238.28	9.31E-54
100	1.9E-04	3.8E-02	428.43	3.56E-95	667.05	4.38E-147	238.61	7.89E-54
200	1.0E-04	1.9E-02	428.38	3.67E-95	667.12	4.24E-147	238.74	7.41E-54
400	5.0E-05	9.5E-03	428.39	3.64E-95	667.15	4.16E-147	238.76	7.32E-54
600	3.0E-05	6.3E-03	426.30	1.04E-94	667.16	4.14E-147	240.86	2.55E-54
800	2.0E-05	4.8E-03	415.16	2.77E-92	667.17	4.12E-147	252.01	9.45E-57
1000	2.0E-05	3.8E-03	428.40	3.63E-95	667.17	4.12E-147	238.78	7.27E-54
1200	2.0E-05	3.2E-03	405.42	3.65E-90	667.17	4.11E-147	261.76	7.10E-59
1400	1.0E-05	2.7E-03	394.96	6.90E-88	667.18	4.11E-147	272.22	3.73E-61
1600	1.0E-05	2.4E-03	415.16	2.76E-92	667.18	4.11E-147	252.02	9.43E-57
1800	1.0E-05	2.1E-03	426.31	1.03E-94	667.18	4.11E-147	240.87	2.54E-54
2000	1.0E-05	1.9E-03	428.40	3.63E-95	667.18	4.10E-147	238.78	7.26E-54

Analyses were carried out as described in Supplementary Table 4, but a genome-wide data set of ~56,000 SNPs was used. In each case, the model incorporating proportional selection effects (w = s*β) showed the best fit to the AF data. Northern- and Southern-European allele frequencies are estimated from the MIGen Harps (NEur) and Regicor (SEur) datasets.

Supplementary Table 12. Likelihood ratio tests and maximized values of s for models of drift and drift plus selection in genome-wide data using the POPRES dataset (UK individuals vs. Italian individuals)

T (gener-ations)	s (w=s)	s (w=sβ)	LRT statistic: w=s vs. Drift	LRT p-value: w=s vs. Drift	LRT statistic: w=sβ vs. Drift	LRT p-value: w=sβ vs. Drift	LRT statistic: w=sβ vs. w=s	LRT p-value: w=sβ vs. w=s
20	1.7E-03	3.3E-01	904.78	8.97E-199	1289.25	2.45E-282	384.47	1.32E-85
50	7.0E-04	1.3E-01	905.39	6.61E-199	1299.73	1.29E-284	394.34	9.39E-88
100	3.5E-04	6.6E-02	905.61	5.93E-199	1299.95	1.16E-284	394.35	9.37E-88
200	1.7E-04	3.3E-02	905.33	6.81E-199	1300.06	1.10E-284	394.73	7.73E-88
400	9.0E-05	1.6E-02	904.65	9.56E-199	1300.11	1.07E-284	395.46	5.36E-88
600	6.0E-05	1.1E-02	904.67	9.48E-199	1300.13	1.06E-284	395.46	5.36E-88
800	4.0E-05	8.2E-03	900.15	9.11E-198	1300.14	1.05E-284	399.99	5.52E-89
1000	3.0E-05	6.6E-03	888.89	2.55E-195	1300.15	1.05E-284	411.26	1.95E-91
1200	3.0E-05	5.5E-03	904.69	9.40E-199	1300.15	1.05E-284	395.47	5.35E-88
1400	2.0E-05	4.7E-03	871.63	1.44E-191	1300.15	1.05E-284	428.52	3.41E-95
1600	2.0E-05	4.1E-03	900.16	9.05E-198	1300.16	1.05E-284	399.99	5.53E-89
1800	2.0E-05	3.6E-03	904.69	9.37E-199	1300.16	1.04E-284	395.47	5.35E-88
2000	2.0E-05	3.3E-03	885.23	1.60E-194	1300.16	1.05E-284	414.93	3.10E-92

Analyses were carried out as described in Supplementary Table 11, but the Northern- and Southern-European allele frequencies were estimated using UK and Italian individuals from the POPRES dataset.

Supplementary Table 13. Sign test and mean NEur – SEur AF difference tests for directly genotyped height-associated SNPs or height-associated SNPs with proxies

Supplementary Table 13A – MIGen

Directly Genotyped		**Proxies**	
Sign Test (N > S)	p-value	Sign Test (N > S)	p-value
35 of 55	0.058	50 of 84	0.10
Mean NEur-SEur AF	p-value	Mean NEur-SEur AF	p-value
0.013	0.023	0.011	0.0077

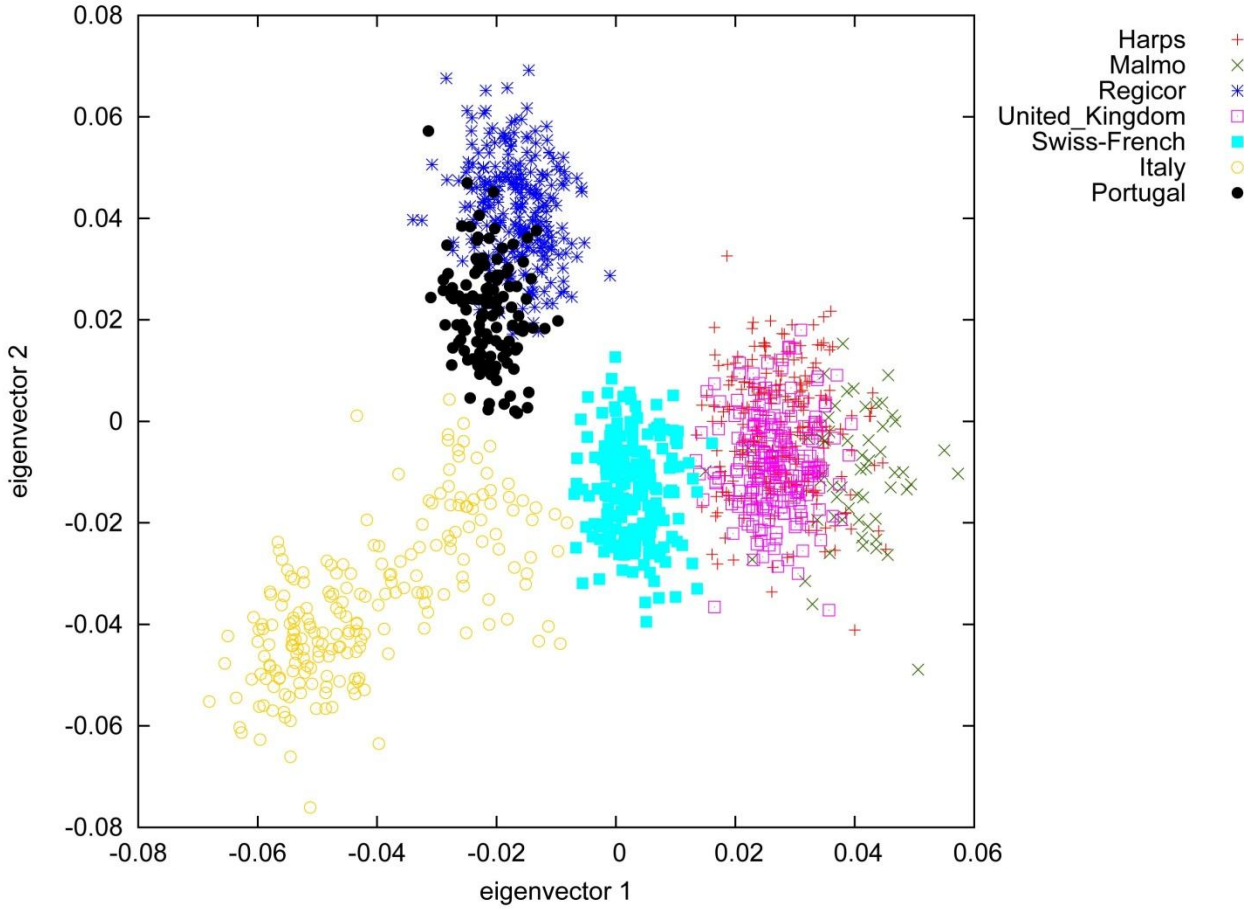
Supplementary Table 13B – POPRES

Directly Genotyped		**Proxies**	
Sign Test (N > S)	p-value	Sign Test (N > S)	p-value
23 of 30	0.0052	47 of 79	0.11
Mean NEur-SEur AF	p-value	Mean NEur-SEur AF	p-value
0.025	0.0028	0.014	0.025

Sign test and mean NEur – SEur AF difference statistics and p-values for directly genotyped height SNPs and proxies to original height SNPs, within the (a) MIGen (Harps vs. Regicor) and (b) POPRES (UK vs. Italy) datasets. NEur, Northern European. SEur, Southern European. AF, allele frequency.

Supplementary Figures and Legends

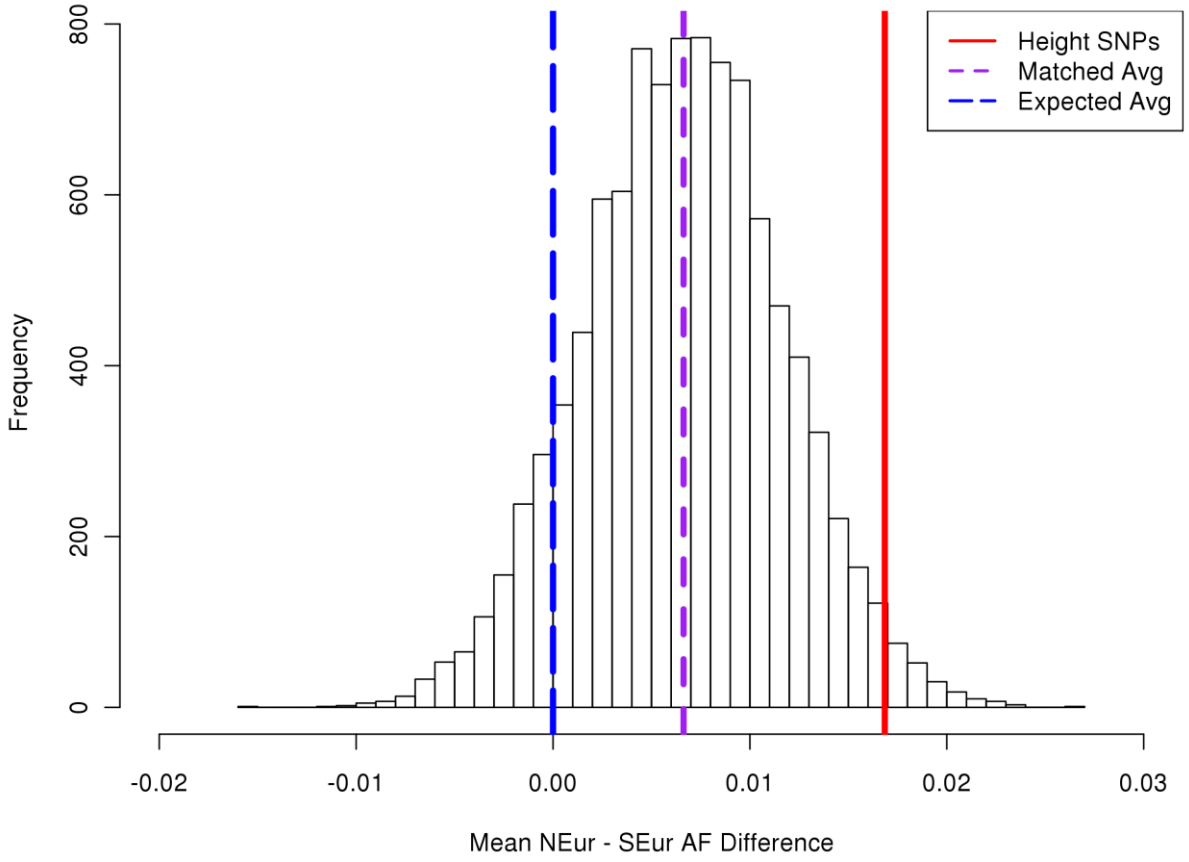
Supplementary Figure 1



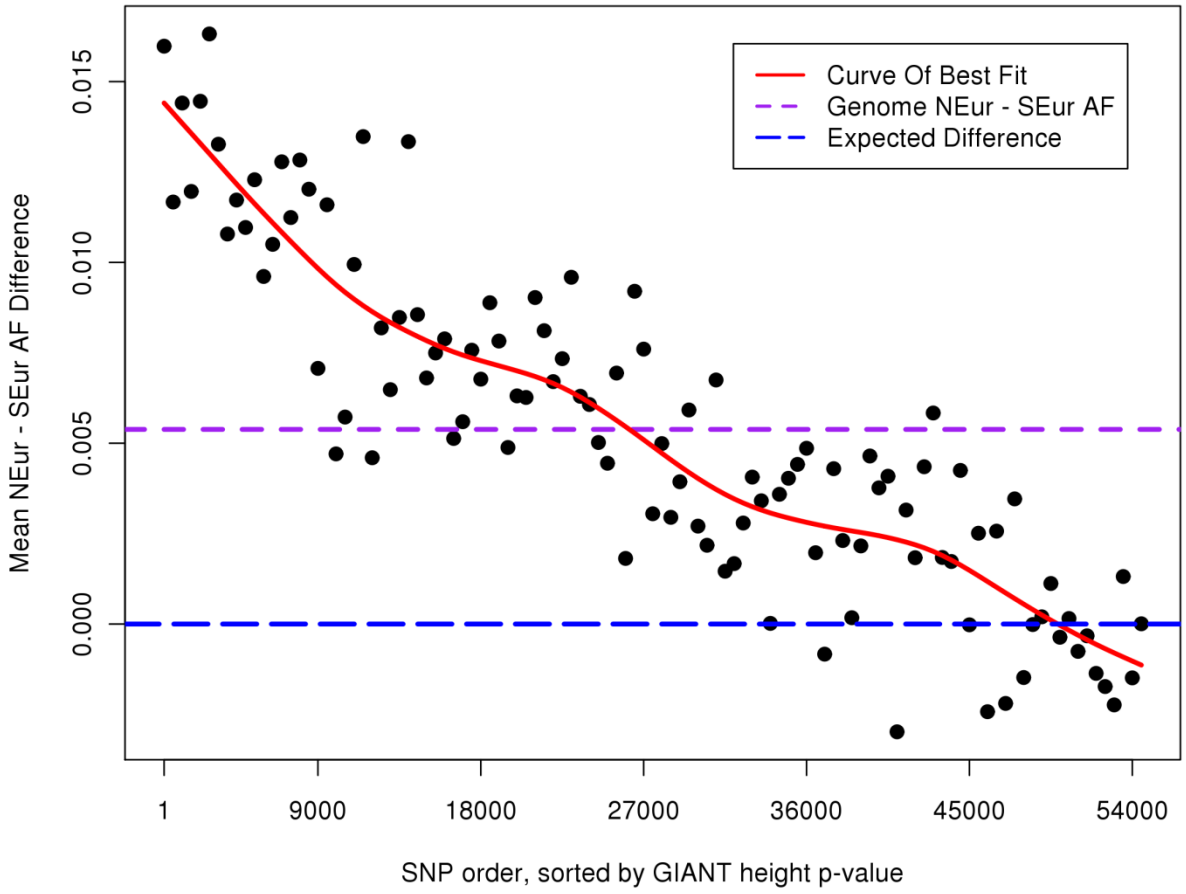
Supplementary Figure 1. PCA plot of NEur and SEur individuals from the MIGen and POPRES datasets

Plot of eigenvector 1 vs. eigenvector 2 from principal component analysis (PCA) on both MIGen (Individuals of Northern European ancestry from U.S. [Harps], from Sweden [Malmo], and from Spain [Regicor]) and POPRES (Individuals from UK, Switzerland-French, Italy, and Portugal) datasets, after outlier removal (see Materials and Methods).

Supplementary Figure 2a

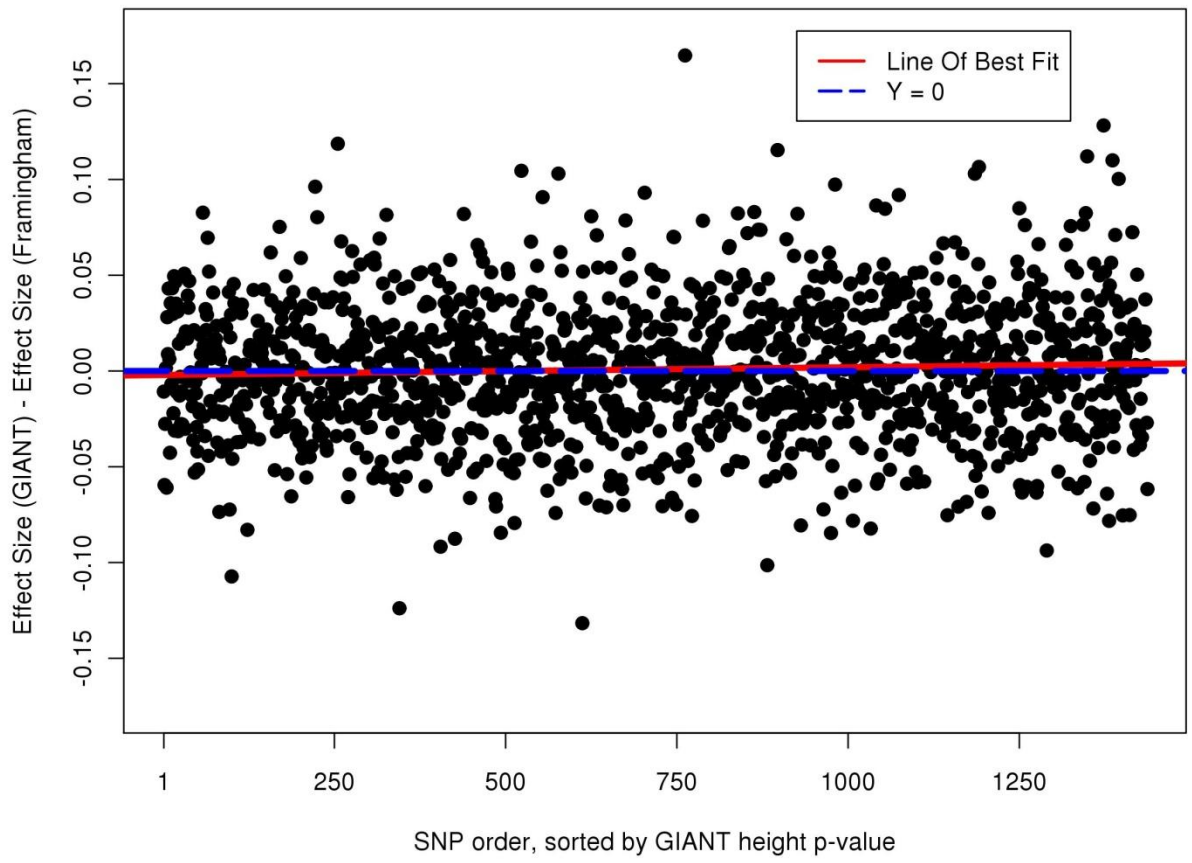


Supplementary Figure 2b



Supplementary Figure 2. Mean NEur – SEur AF difference of height SNPs, matched SNPs and genome-wide SNPs using POPRES data.
a, Analysis of mean NEur – SEur AF difference of 109 height SNPs (solid red line) versus 10,000 sets of randomly-drawn, frequency-matched SNPs. Shown in purple is the mean value across the 10,000 permutations, and in blue the expected mean difference. NEur and SEur AF were estimated using POPRES dataset. The height-increasing allele of the 109 height SNPs is significantly more common in NEur compared to the genome-wide data ($p = 0.021$). **b**, Mean NEur – SEur AF difference for sets of 500 independent ($r^2 < 0.1$) SNPs across the genome using POPRES data. SNPs were sorted by GIANT height association p-value. Shown in red is the curve of best fit, in purple the genome-wide mean NEur – SEur AF difference, and in blue the expected mean difference (y=0). NEur, Northern European. SEur, Southern European. AF, allele frequency.

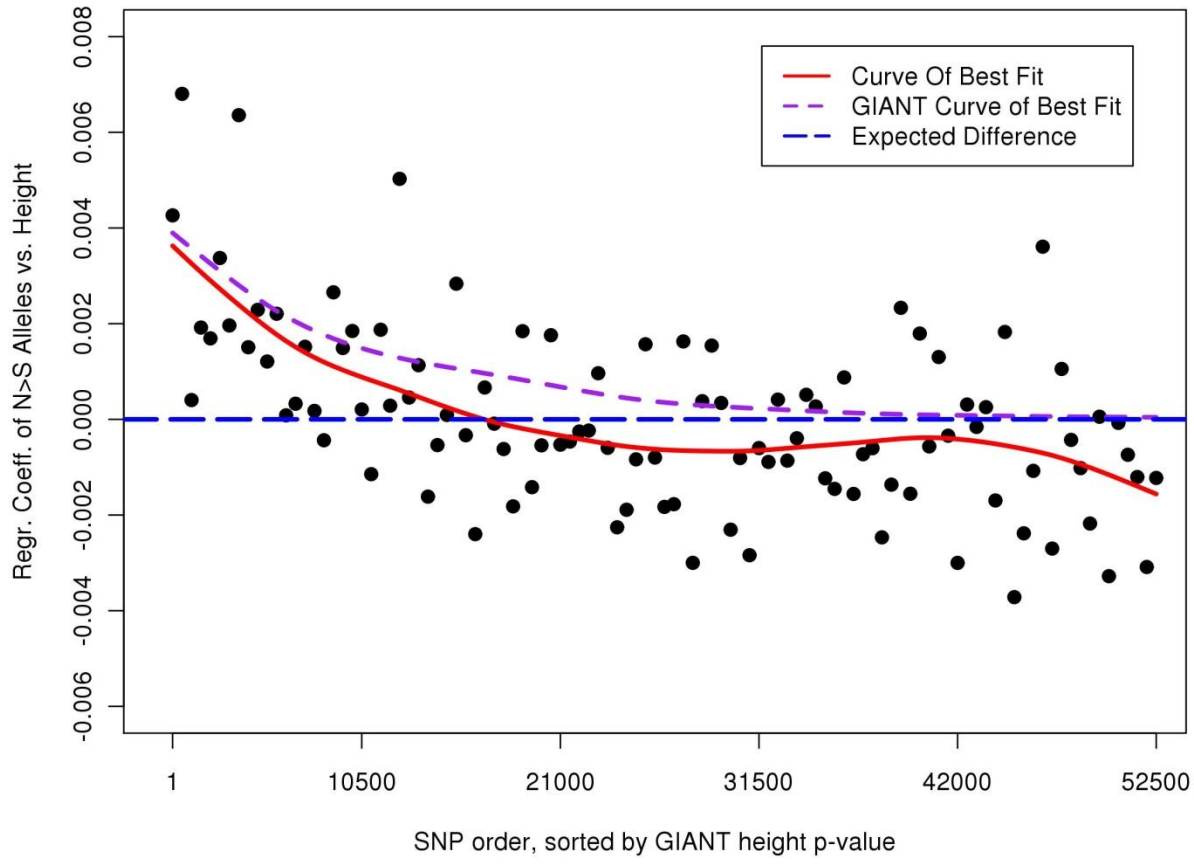
Supplementary Figure 3



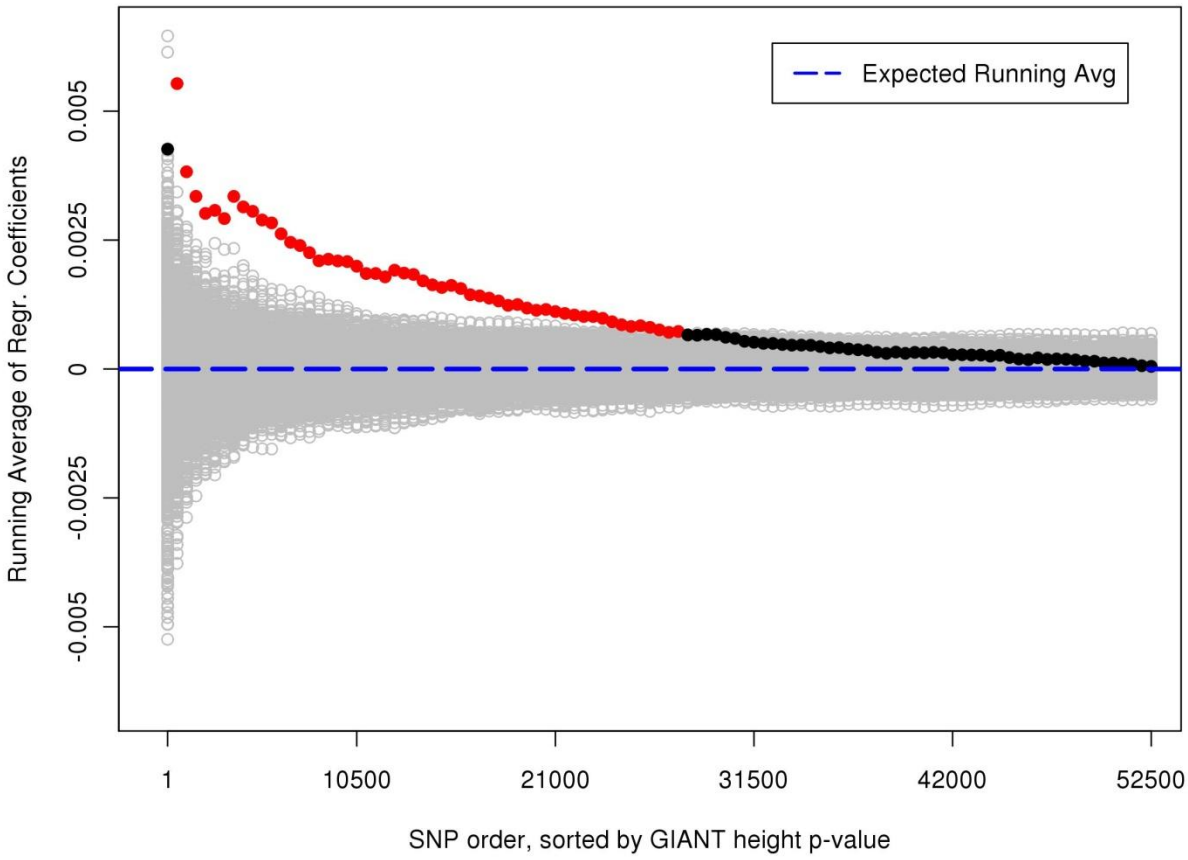
Supplementary Figure 3. GIANT effect sizes versus FHS within-sibship regression coefficients.

For each SNP in a set of strictly independent ~1,400 SNPs ($r^2 < .1$ and distance >1 Mb) showing the strongest association to height, we calculated the FHS within-sibship regression coefficient as described in Figure 2a. For the same set of SNPs, the GIANT effect sizes were determined by meta-analyzing the GIANT cohorts without the FHS dataset. Overall, the GIANT effect sizes are not significantly different from the FHS within-sibship regression coefficients ($p = 0.3622$ by paired t-test). Line of best fit is shown in red, $y = 0$ in blue.

Supplementary Figure 4a

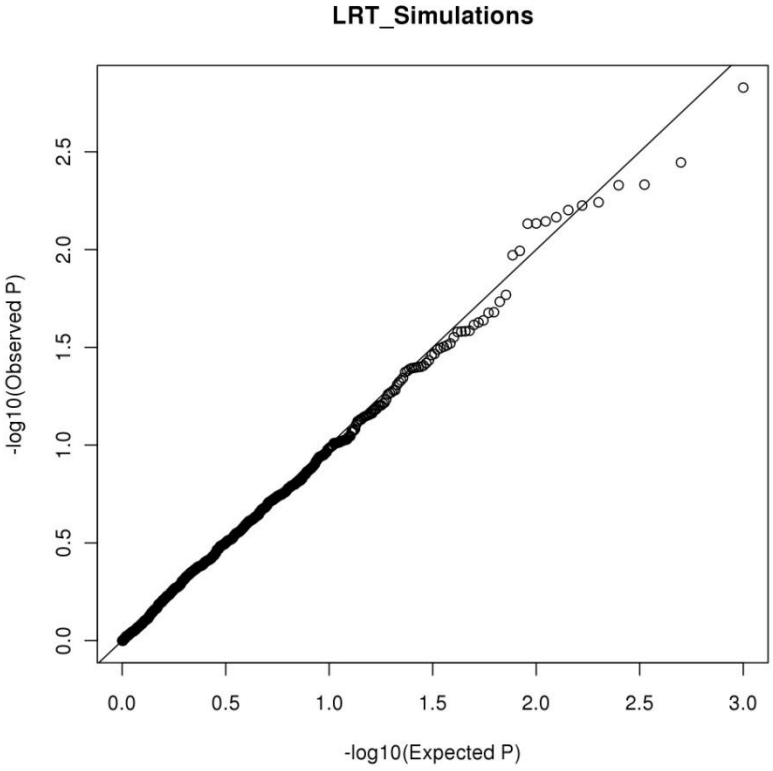


Supplementary Figure 4b



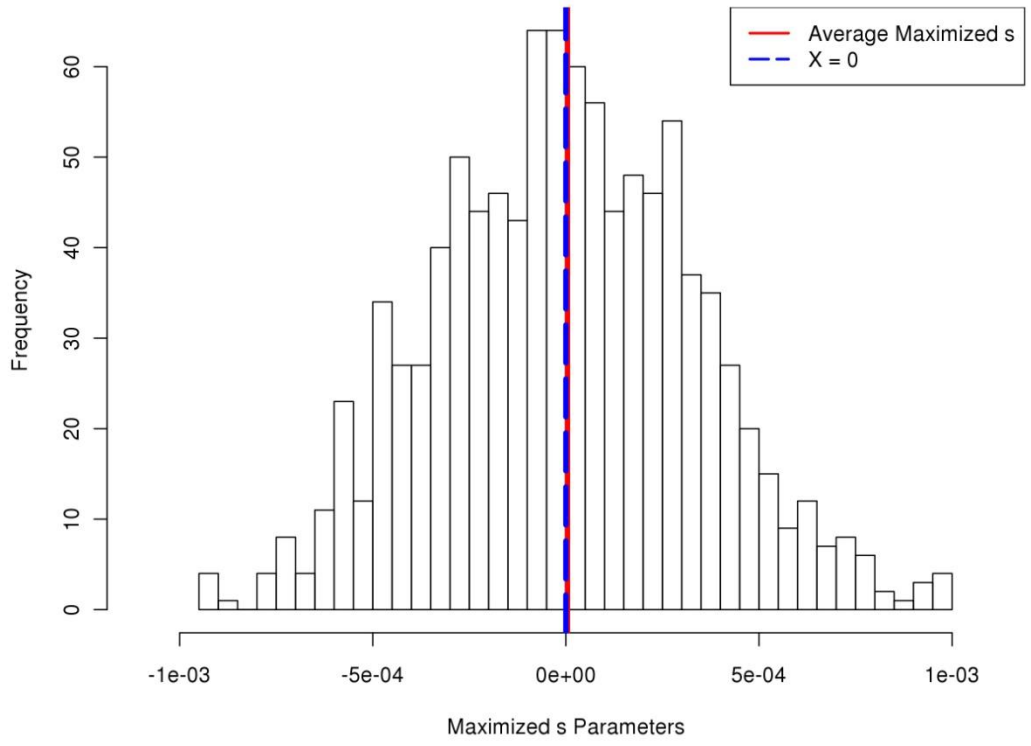
Supplementary Figure 4 – Within-family analyses of height and the Northern-predominant alleles across the genome using POPRES data.
Within-family analyses of height and the Northern-predominant alleles across the genome in the POPRES dataset. Analyses were conducted as described in Figure 3, but using the POPRES dataset to define the Northern-predominant allele. **a**, Regression coefficients are plotted on the y-axis for groups of 500 independent SNPs on the x-axis, with the curve of best fit shown in red, the curve of best fit for the GIANT effect sizes in purple, and y=0 in blue. **b**, Running averages of the regression coefficients (red and black filled circles) are plotted on the y-axis and compared against the running averages of regression coefficients from 1,000 analyses where phenotypes were permuted within-sibships (grey open circles). Observed data points are colored black if they are less extreme than 0.01% of the permuted values. Blue dashed line is y=0.

Supplementary Figure 5



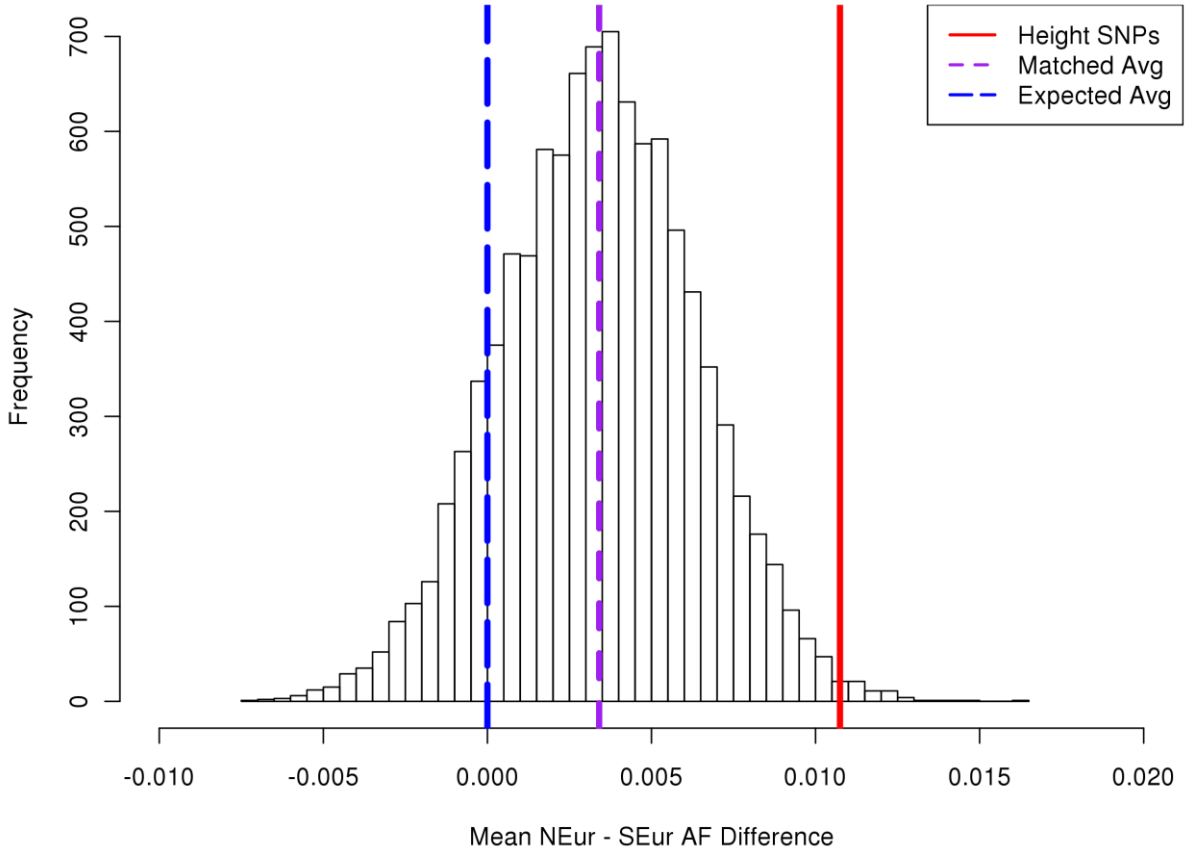
Supplementary Figure 5. Quantile-quantile (QQ)-plot of LRT p values in 1,000 simulated datasets generated under the null model of no selection.
1,000 simulations were conducted using the ~56,000 SNP MIGen dataset where for each simulation, GIANT effect size directions were randomly flipped so that ~50% were in the opposite direction than from the original data. For each of these simulations, we compared the fit to data using models incorporating selection ($w = s\beta$) vs. drift alone using the likelihood ratio test (LRT) as described in Table 1. Over 1,000 simulations, the maximized s parameters were normally distributed around 0 (Supplementary Figure 6), and the distribution of LRT p-values were uniform, consistent with accepting the null hypothesis of drift alone (i.e. no selection). The false discovery rate at $p < 0.05$ within these 1,000 simulations was 4.7%.

Supplementary Figure 6

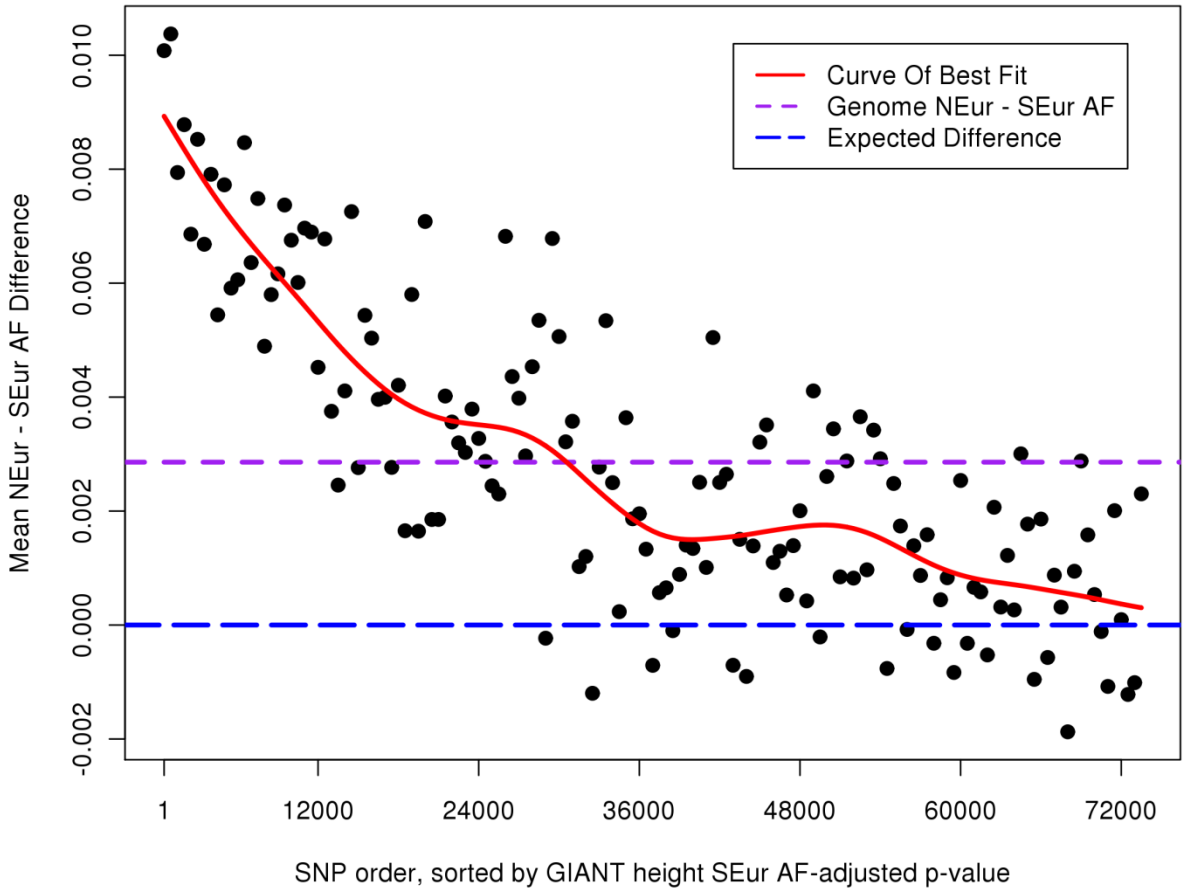


Supplementary Figure 6. Distribution of the maximum likelihood estimate of s in 1,000 simulated datasets generated under the null model of no selection.
Histogram of the maximized s parameters from the 1,000 simulations described in Supplementary Figure 5. The mean and s.d. of the 1,000 maximized s estimates are 4.00×10^{-6} and 3.39×10^{-4}, respectively. Mean maximized s estimate is shown in red, and x=0 in blue.

Supplementary Figure 7a

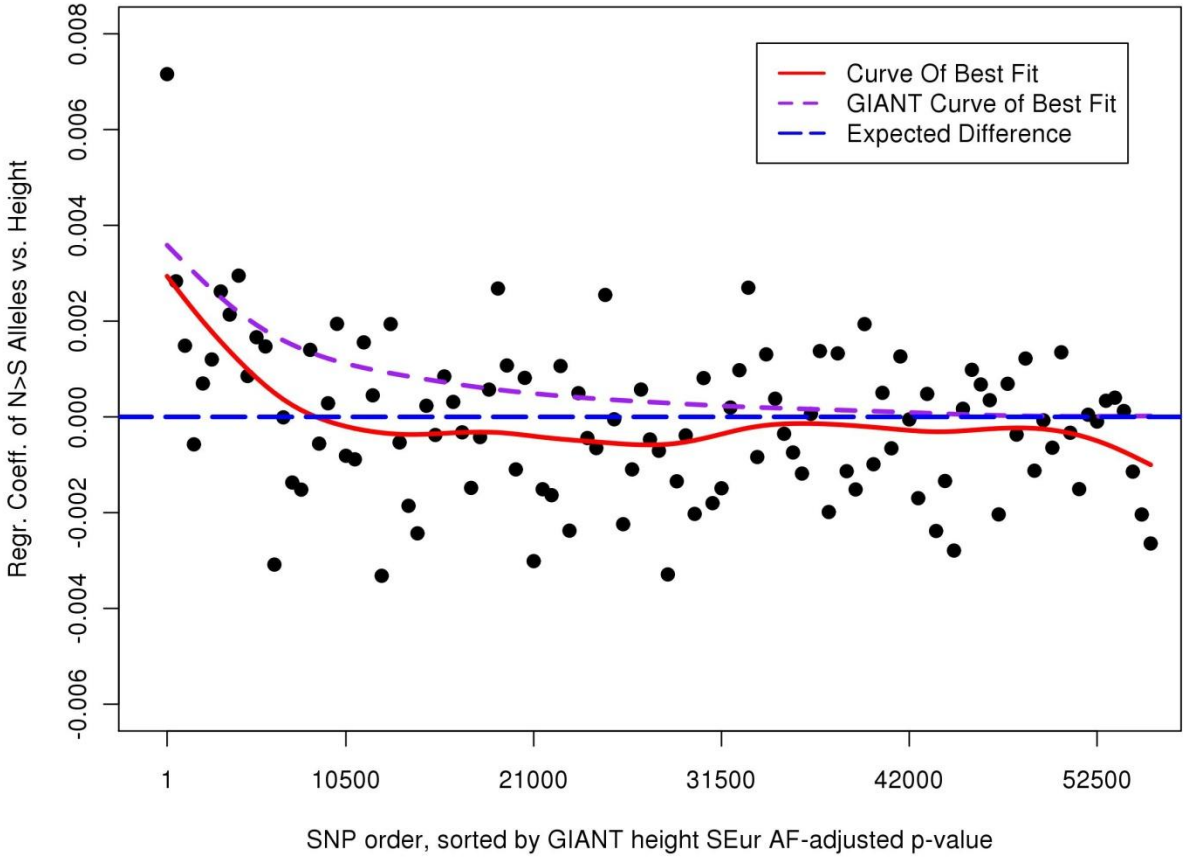


Supplementary Figure 7b

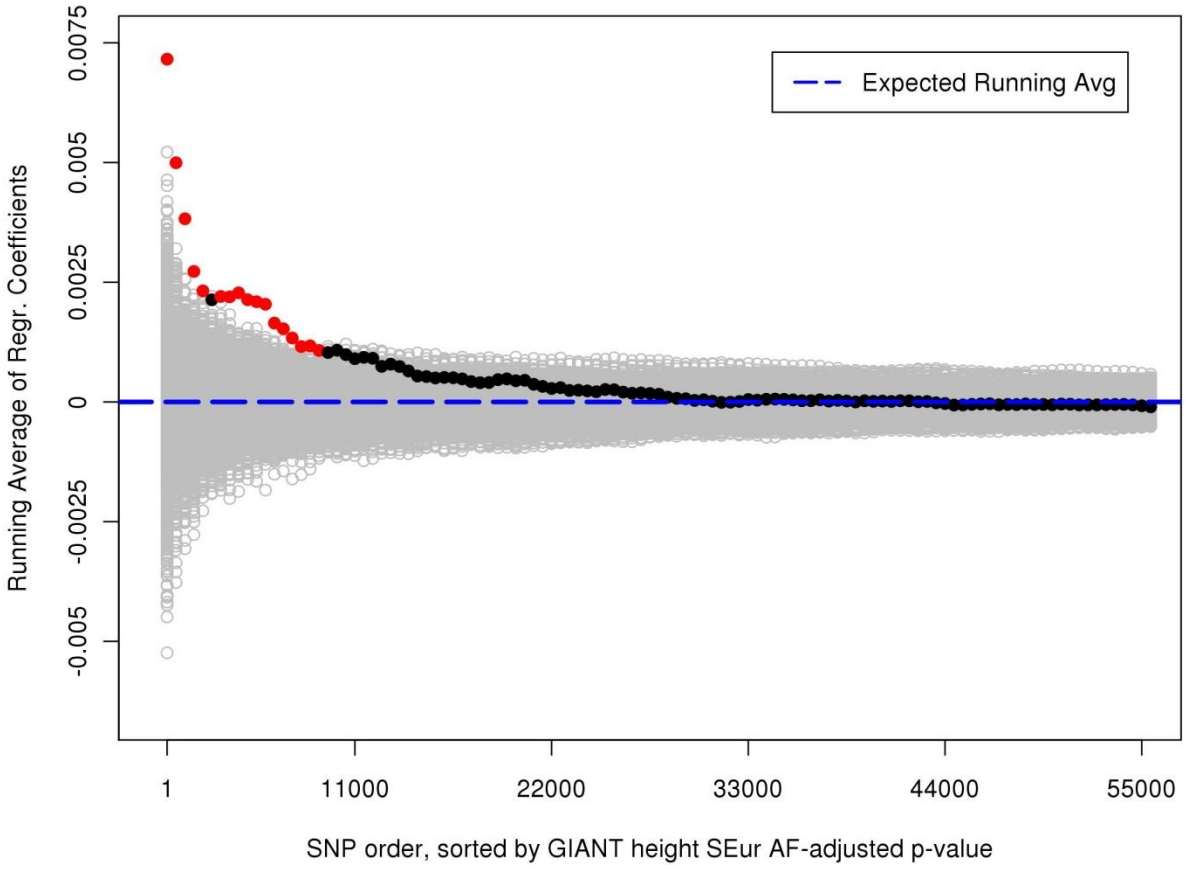


Supplementary Figure 7. Mean NEur – SEur AF differences for height SNPs, matched SNPs and genome-wide SNPs, when SNPs are ascertained by SEur AF-adjusted p-values. **a**, The mean NEur – SEur AF difference in MIGen of 185 height SNPs, identified by the SEur AF-adjusted p-value dataset (see Supplementary Methods) are shown in red, compared to 10,000 sets of randomly-drawn, frequency-matched SNPs. Shown in purple is the mean value across the 10,000 permutations, and in blue the expected mean difference (y=0). The height increasing allele of the 185 height SNPs is significantly more common in NEur than the genome-wide average ($p = 0.0064$), suggesting that any ascertainment bias of height-associated SNPs due to largely NEur ancestry of the GIANT consortium does not explain our results. **b**, Mean NEur – SEur AF difference for sets of 500 independent ($r^2 < 0.1$) SNPs across the genome ordered by SEur AF-adjusted p-vales. SNPs were sorted by SEur AF-adjusted p-vales (see Materials and Methods). Shown in red is the curve of best fit, in purple the genome-wide mean NEur – SEur AF difference, and in blue the expected mean difference (y=0). NEur, Northern European. SEur, Southern European. AF, allele frequency.

Supplementary Figure 8a

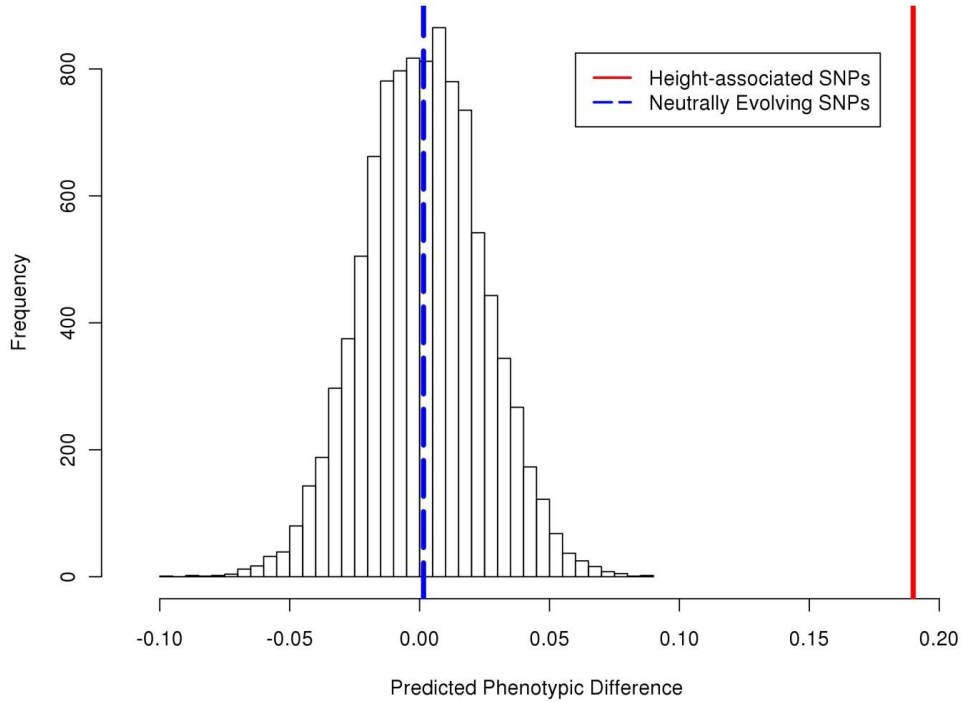


Supplementary Figure 8b



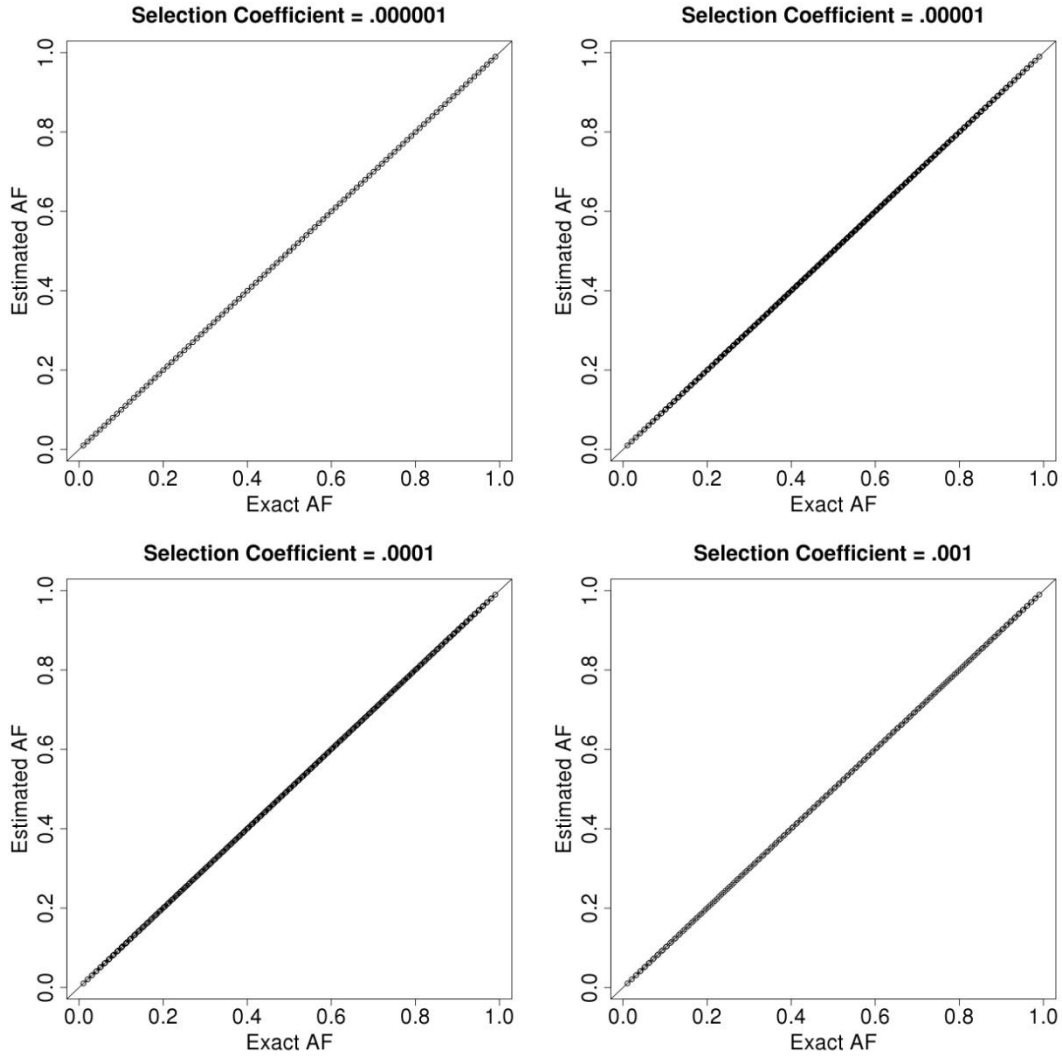
Supplementary Figure 8 – Within-family analyses of height and the Northern-predominant alleles across the genome with SNPs ranked by SEur AF-adjusted p-value.
We performed within-family association analyses of height and the Northern-predominant alleles across the genome, ranking SNPs by the SEur AF-adjusted p-values (see Supplementary Methods), and using AF data from MIGen. Analyses were conducted as described in Figure 3, but using the MIGen dataset to define the Northern-predominant allele, and ranked by SEur AF-adjusted GIANT height p-values. **a**, Regression coefficients are plotted on the y-axis for groups of 500 independent SNPs on the x-axis, with the curve of best fit shown in red, the curve of best fit for the GIANT effect sizes in purple, and y=0 in blue. **b**, Running averages of the regression coefficients (red and black filled circles) are plotted on the y-axis and compared against the running averages of regression coefficients from 1,000 analyses where phenotypes were permuted within-sibships (grey open circles). Observed data points are colored black if they are less extreme than 0.01% of the permuted values. Blue dashed line is y=0. SEur, Southern European. AF, allele frequency.

Supplementary Figure 9



Supplementary Figure 9. Population phenotypic differentiation based on top height-associated SNPs and 10,000 simulations of neutrally evolving SNPs.
Given a set of independent SNPs, we calculate the predicted population phenotypic differentiation by multiplying the effect size (in units of standard deviations; 1 standard deviation is approximately 6.5 cm, or 2.5 inches) of each height-increasing allele by the difference in allele frequency between NEur and SEur, and summing this over all the SNPs in the set. Based on ~1,400 SNPs with the best evidence of association with height from the GIANT dataset (see Supplementary Methods), we compared the population phenotypic differentiation predicted to be accounted for by these height-associated SNPs (red solid line) to that produced by 10,000 sets of randomly-drawn, frequency-matched SNPs presumed to be under drift (histogram, mean indicated by blue dashed line). The matched SNPs have the same ancestral allele frequency, and absolute magnitude of effect sizes as the height-associated SNPs, and their allele frequencies are drawn from the actual NEur and SEur AF distributions, but they have no bias in the direction of effect with respect to the NEur - SEur AF. The height-associated SNPs produced a predicted phenotypic differentiation significantly greater than that produced by neutrally evolving variants assumed to have the same genetic architecture ($p = 3.9 \times 10^{-17}$, based on the mean and standard deviation for the 10,000 matched sets). This suggests that the observations presented in this study are not simply the result of ascertaining a trait/population pair from the extreme end of a plausibly-sized set of neutrally evolving traits, but rather reflect the effects of selection. NEur, Northern European. SEur, Southern European. AF, allele frequency.

Supplementary Figure 10



Supplementary Figure 10. Comparisons of exact and linearly approximated AF differences. For selection coefficients, s, of 10^{-6} and 10^{-5}, exact AF differences were calculated at starting AFs from .01 to .99 over generation times of 100, 500, 1000, 1500 and 2000. For s = 10^{-4} generation times of 50, 100, 200 and 400 were used, and for s = 10^{-3} generation times of 20 and 50 were used. Linear approximations of these same AF differences were then also calculated as described in section 2.5. The results from these two approaches were then compared against one another, with exactly calculated AF differences on the x-axis and linear approximated AF differences on the y-axis. For all selection coefficients tested, the maximum error was 0.12% (mean error: 0.0152%). AF, allele frequency.

Supplementary Note

1.1. GIANT height association dataset

The GIANT (Genetic Investigation of ANthrometrics Traits) Consortium was a study that meta-analyzed the genome-wide association results from across 46 different cohorts of European descent containing ~129,000 individuals after quality control filters[6]. The cohorts in GIANT were largely European-American and Northern European (predominantly UK, Iceland, Finland, Sweden, Netherlands and Northern Germany) but also included cohorts from Southern Germany, Switzerland, Tyrolia, Croatia, Sardinia, and Spain. For adult human height, the GIANT consortium identified 180 loci that surpassed genome-wide significance[6]. The genome-wide association dataset included the average allele frequency across the 46 cohorts and the evidence of height association for 2,834,209 SNPs. We focused on the subset of the SNPs that were directly genotyped in either the MIGen study[7] or the POPRES dataset[8] (see below). All alleles are reported on the positive strand using HapMap phase 2 CEU panel[9] as reference.

For GIANT authors and affiliations, see section 5.

1.2. European allele frequency datasets

Two datasets were used to estimate Northern- and Southern-European allele frequencies. The first dataset consisted of cohorts from the MIGen (Myocardial Infarction Genetics) Consortium[7], a population based study that combined the genome-wide association study results from 5 different cohorts investigating myocardial infarction. We used 306 individuals of Northern-European ancestry from the United States (Harps) to estimate Northern-European allele frequencies and 270 individuals from Spain (Regicor) to estimate Southern-European allele frequencies. The second dataset consisted of individuals from POPRES (POPulation REference

Sample[8]), a study that collected ~4,000 individuals from across Europe and includes a public dataset that contains allele frequency information for individuals of various European ancestries. Individuals identified as being from the UK (N=388) were used to estimate Northern-European allele frequencies, and individuals identified as being from Italy (N=225) were used to estimate Southern-European allele frequencies.

We applied a series of quality control measures equally to the SNP data from both datasets. Only directly genotyped SNPs were used. SNPs were removed if the minor allele frequency in either datasets was less than 5%, if the genotype call rate was less than 90%, or if the SNP was out of Hardy-Weinberg equilibrium ($p < 1x10^{-6}$). SNPs that were not assayed in both the Northern- and Southern-European populations were also removed. Individuals were removed if the genotype call rate was less than 95%. Genome-wide IBD estimates were determined using PLINK v1.07 (ref 10) for all possible pairs of individuals within each population, and related individuals were removed so that no pair of individuals had pi hat estimates greater than 5%. Ancestry of the remaining individuals was then determined through PCA analysis, and the outliers from the 4 main clusters (Harps, Regicor, UK and Italy) were removed. Within the POPRES dataset, a random sample of UK individuals was used so that the sample size matched the Italian sample size. Non-informative SNPs (Northern- to Southern-European allele frequency difference exactly equaled 0; < 1% of total SNPs) were dropped. SNP- and individual-level quality controls were performed using PLINK v1.07 (ref 10); PCA analysis was conducted using Eigenstrat v3.0 (ref 11).

In the end, a total of 257 individuals from Harps and 254 individuals from Regicor from the MIGen study were available for estimating Northern- and Southern-European allele frequencies at 603,276 SNPs; 208 individuals from UK and 208 individuals from Italy from the

POPRES dataset were available for estimating Northern- and Southern-European allele frequencies at 298,691 SNPs.

For additional pairwise comparisons between different European populations, we also utilized the individuals from Switzerland (French) and Portugal from the POPRES dataset, as well as Swedish individuals from the MIGen Malmo dataset. These cohorts were subjected to the same quality control measures as described above, and were down-sampled as needed in order to make the appropriate comparison in our analysis.

1.3. Framingham Heart Study

The Framingham Heart Study is a multi-generational family-based cohort based in Framingham, Massachusetts, which has been actively collected since 1951 (ref 12). Sibs based on pedigree information were confirmed to be in the same sibship if the pair-wise IBD estimates (calculated using PLINK v1.07) showed that the proportion of the genome with IBD = 2 was between 0.10 and 0.42. In total, 1,761 nuclear sibships were identified, including 4,819 individuals. Furthermore, due to differences in final SNP sets used between FHS and GIANT, there are 314,299 and 277,214 SNPs available with frequency data from MIGen and POPRES, respectively. Only SNPs directly genotyped in FHS were used. Quality control protocol conducted on the FHS dataset is described previously[13].

2 Modeling genetic drift and selection

To model the effect of drift and selection on the observed Northern- to Southern-European frequency differences, we first estimated the expected amount of allele frequency

differences that could be attributed to selection using the following equation (see section 4 for derivation):

$$\Delta \mathrm{AF}_{\mathrm{Sel}} \approx T \times \left(\frac{wp^2 + wp + p}{1 + 2wp} - p \right)$$

where p is the ancestral allele frequency (estimated as the average of Northern- and Southern-European allele frequency), T is the number of generations since the two populations have split, and w is the selective pressure experienced by the population under different models of ongoing selection.

Note that the above equation for changes of allele frequency is only an approximation, as the changes in allele frequency are also a function of the allele frequency itself. However, this effect is negligible when the changes in allele frequency are very small between generations, as is the case here, since $(1+x)^T \approx 1+Tx$ when $Tx<<1$. To confirm the validity of this assumption for the ranges of selection coefficients that we estimated, we calculated the exact changes in allele frequency expected for selection coefficients of 10^{-5} and 10^{-6}, for starting allele frequencies between .01 to .99 at generation times of 100, 500, 1000, 1500 and 2000. For a selection coefficient of 10^{-4}, generation times of 50, 100, 200 and 400 were used, and for a selection coefficient of 10^{-3}, generation times of 20 and 50 were used. At each generation, we calculate the expected allele frequency for the next generation conditional on the selection coefficient and the allele frequency of the current generation. We then compared the exact calculations with that obtained from the linear approximation (calculated above; Supplementary Figure 10). For all selection coefficients tested, the maximum error ((exact allele frequency - approximated allele frequent) / exact allele frequency) was 0.12% (mean error: 0.0152%).

Based on these results, we conclude that our approximation is sufficiently accurate for very small changes in allele frequency. This simplifying (and computationally less intensive)

approximation was used to produce the LRT results in Supplemental Tables 3-12. Note that results presented in Table 1 were obtained using the exact calculation.

We examined two different models of selection: 1. constant selection, where w was set to a constant selective parameter, s; 2. selection modulated by effects on height, where w was set to the product of a constant selective parameter and the SNP's effect on height (obtained from GIANT dataset, in units of s.d.), $s * \beta$. We then determine ΔAF_{Sel} over a range of selective parameters (0 to 0.1) across multiple generational times since divergence of the two populations (20 to 2,000). Though NEur and SEur populations are unlikely to have diverged as recently as 20 generations ago (~400-500 years), these values of T were included to account for the likely migration between NEur and SEur since divergence, which would decrease the effective T and hence increase the estimate of s. We performed a grid-like search over both parameter spaces: selection parameters were stepped through by increments of $1x10^{-4}$ from 0.01 to 0.1, increments of $1x10^{-5}$ from $1x10^{-5}$ to 0.01 and increments of $1x10^{-6}$ from 0 to $1x10^{-5}$, and generational times were stepped through by increments of 100 generations from 100 to 2000. For each combination of parameters, we subtracted the change in allele frequency attributable to selection from the observed Northern- to Southern-European allele frequency differences, and determined the likelihood of observing the remaining allele frequency differences due to drift as described above. The parameters that maximized the likelihood of each model for each generational time since divergence were determined. The maximum likelihood parameter for all three models incorporating selection were compared against one another as well as the model with drift-alone, in order to determine the model that best fit our observed data using the likelihood ratio test (LRT). The likelihood ratio statistic (twice the difference in negative log likelihoods) was compared with a χ^2 distribution with the degrees of freedom equal to the difference in the

number of free parameters. We also explored a third model, $w = s_1 + (s_2 * \beta)$. However, in this case the maximum likelihood estimate for s_1 is zero across all generational times tested, so this class of models was not considered further.

We performed a number of simulations to test the behavior of our model. Specifically, we tested the performance of the LRT in data sets where we randomly reversed half of the signs of the effects on height, thereby creating demographically-matched data sets in which there is no effect of selection (described in section 3.4). We also performed forward simulations of populations under drift with or without selection, to test whether our LRT procedure could accurately estimate the selection parameters, and whether the method had sufficient power to detect widespread weak selection with coefficients in the ranges estimated by our data (described in section 3.5). Finally, in our modeling, we assumed a simplistic process of concurrent selection at many sites, which does not account for the more complex effects of multiple selected loci that ensue as allele frequencies begin to change substantially[14]. However, because the observed frequency differences are typically small (mean frequency difference = ~0.01 even for the most strongly associated SNPs), we can still use our models to roughly estimate the typical selective pressures on height-associated variants that would be consistent with our data.

3.1 Assessing possible ascertainment bias from the largely Northern-European ancestry in GIANT

The bulk of our analysis depends heavily on the GIANT dataset for defining the height-increasing allele and for providing height association p-values. Because GIANT analyzed mostly individuals of Northern European ancestry, under certain scenarios the GIANT consortium could have better power to identify height-associated SNPs that surpass a genome-wide significance

threshold if the height-increasing alleles are more common in Northern-European populations. Specifically, because variance explained is proportional to heterozygosity, the GIANT consortium would have better power to identify SNPs as associated with height if the allele frequencies are closer to 0.5. Thus some variants with different allele frequencies in Northern Europeans and Southern Europeans might have greater likelihoods of being identified as associated with height in a study of Northern Europeans. Note that this potential bias would only be consistent with our results for variants where the height-increasing allele is the minor allele. In our datasets height-increasing alleles actually have equal probability of being the major or the minor allele (MIGen: N = 70 vs. N = 69). Nonetheless, we performed additional analyses to account for this possible ascertainment bias.

We considered whether the results of our analysis would remain the same if the GIANT consortium had been composed entirely of Southern-European populations, and the SNPs had the same effects on height in Northern Europeans and Southern Europeans. To do this, we adjusted the height-association p-value for each SNP in the GIANT dataset by assuming that the allele frequency in GIANT was equal to the estimated Southern-European allele frequency, but effect sizes remained the same. Specifically, for each SNP in the GIANT dataset, we first converted the height-association p-values into quantiles of a standard normal distribution. As the quantiles (or z-statistics) are functions of the effect size (unchanged) and the square root of the heterozygosity in the population, we adjust the GIANT z-statistics by $(pq_{SEur}/pq_{GIANT})^{1/2}$, where p and q are the allele frequencies of the major and minor allele for that SNP. The adjusted z-statistics was then converted into Southern-European frequency-adjusted p-values to obtain the hypothetical evidence of association for each SNP, under the scenario where GIANT had studied predominantly Southern-European individuals.

To recreate a list of height loci that would surpass genome-wide significance in this hypothetical scenario, we then followed the analytical steps described by GIANT [6]. Briefly, we clumped our new dataset with an $r^2 \geq 0.1$ using the most significantly associated SNP as our lead SNP in each region, and then pruned remaining SNPs within 0.5 Mb of one another, preferentially keeping the SNPs with best association to height within each clump. We identified SNPs with Southern-European frequency-adjusted p-values lower than that of the least significantly associated height loci among the published 180 loci in the original GIANT dataset. This process generated a list of 185 SNPs (using frequency data from MIGen) and 156 SNPs (using frequency data from POPRES) that in theory would have passed genome-wide significance threshold had the GIANT consortium used predominantly individuals from Southern Europe.

We repeated all of our analyses using the new set of height SNPs and also using a new p-value-ordered genome-wide set of SNPs based on Southern-European frequency-adjusted p-values (Supplementary Table 1 and Supplementary Figures 4-5). In general, we observed the same pattern of height-increasing allele being more prevalent in Northern Europeans than in Southern Europeans, suggesting that the variant ascertainment due to the largely Northern-European ancestry of the GIANT consortium did not confound our results.

3.2 HapMap SNP ascertainment bias

We also considered the effects of identifying height-associated SNPs from the set of SNPs in HapMap, which were ascertained in part by sequencing in Northern- but not Southern-European samples. We used data from the 1000Genomes Project[15] to simulate two different SNP ascertainment schemes. We catalogued all SNPs present in the low-pass whole genome

sequence data in either four unrelated CEU samples from 1000Genomes or in two CEU, 1 YRI and 1 CHB sample. We then drew SNPs from this pool, assembling 1,000 sets of SNPs matched to the ~1,400 height-associated SNPs by their Northern-European minor allele frequency in the 1000Genomes GBR panel. We also assigned the "height-increasing" allele of each matched SNP to be either the GBR major or minor allele, depending on whether the actual height-associated SNP to which it was matched was the Northern-European major or minor allele. We then calculated Northern- to Southern-European allele frequency differences for the actual set of height-increasing alleles and for the 1000 matched sets of "height-increasing" alleles. For neither ascertainment scheme was the frequency difference of any of the matched sets of "height-increasing" alleles greater than the frequency difference for the actual height-increasing alleles. We also calculated the mean and standard deviation of the Northern- to Southern-European allele frequency difference data for the matched sets of SNPs, and used these to calculate a Z-score for the value of frequency difference for the actual height-increasing alleles. The Z-scores were 6.04 and 6.05 for the two ascertainment schemes, corresponding to p values of 7.5×10^{-10} and 7.3×10^{-10}.

3.3 Phenotype ascertainment bias

Another potential bias to our analysis is our ascertainment on a phenotype known to be differentiated between Northern and Southern Europe. As had been discussed by Orr[16], because we selected a phenotype known to be differentiated between two populations, it might not be surprising that we observed more height-increasing alleles in the taller population, when compared to expected parity. We addressed this potential ascertainment bias by demonstrating that the population height differences between Northern and Southern Europeans are extremely

unlikely to be obtained due to just the effects of genetic drift alone, given the known genetic architecture of height.

We performed 10,000 neutral trait simulations starting with the set of 1,437 most strongly height-associated SNPs described in Online Methods. For each simulation, we randomly selected a set of 1,437 variants in the genome, each matched to the corresponding height-associated SNP by estimated ancestral allele frequency (the average of Northern- and Southern-European allele frequency estimates). Each of these randomly drawn frequency-matched variants was assigned the height effect size from the height-associated variant to which the randomly-drawn variant was matched. We then calculated the level of population phenotypic differentiation that would be predicted to arise from drift, based on the Northern- to Southern-European allele frequency difference of the randomly-drawn SNPs and their assigned effect sizes. We calculate this as: Phenotypic differentiation = $\Sigma \beta$ * (NEur-SEur AF). The distribution of phenotypic differentiation over 10,000 sets of matched SNPs is then compared to the phenotypic differentiation calculated using the actual height SNPs. Based on the distribution of phenotypic differentiation for randomly-matched SNPs, we observed that the actual height SNPs are ~8.3 standard deviations away from the mean (Supplementary Figure 9), corresponding to a probability of 10^{-17} of observing this strong a phenotypic differentiation between Northern and Southern Europe in a neutrally evolving trait with the genetic architecture of height. In other words, our observed result in height would still be statistically significant after correction for testing multiple phenotypes even had we ascertained height as the most differentiated phenotype among ~10^{16} neutrally evolving phenotypes.

3.4 Randomized GIANT effect size direction LRT simulations

To test whether our LRT procedure has the appropriate statistical properties, we first estimated the type-1 error rate of our procedure. We started with the actual Northern- and Southern-European allele frequency data and GIANT effect sizes for the set of 1,437 SNPs described in Online Methods, and generated 1,000 matched data sets where there is no effect of selection on the height SNPs. Specifically, for each matched data set, the directions of the GIANT effect sizes for a random ~50% of the analyzed SNPs were reversed, thereby eliminating selection, but retaining all of the other features of our observed data set. We then performed our analyses, comparing a model of $w = s*\beta$ vs. a model of drift alone, and estimated the maximum likelihood estimates of s and calculated the corresponding LRT p-values. If our method were well-behaved, we expect that only ~5% of the simulations should have p-values < 0.05, and the estimated selection parameters should be normally distributed around zero, with magnitudes much less than we observed in the real data. In 1,000 matched data sets, the false discovery rate was ~4.7% (see Supplementary Figure 5 for QQ-plot for p-values), the estimated selection coefficients were normally distributed around zero, and were typically at least an order of magnitude lower than those estimated from the actual data (Supplementary Figure 6). Thus, our approach has the appropriate type-1 error rate on data sets directly comparable to our real data, and, under the null, produces an unbiased set of estimated selective coefficients.

3.5 Forward genetic drift simulations

To test whether our LRT procedure could accurately estimate selection parameters in the ranges that we observed, and whether our method had sufficient power to detect widespread weak selection with coefficients in the ranges estimated by our data, we conducted forward simulations of drift and selection. We used the average allele frequencies of Northern and

Southern Europeans for ~56,000 independent SNPs genome-wide, representing an ancestral population, as the starting point for our simulations. The ancestral population was divided into three equal daughter populations of size N_e. The SNPs in the first of these simulated ancestral populations underwent drift with no selection. The SNPs in the second population underwent both drift and selection (with selective coefficients proportional to effect size, $w = s*\beta$). In the third population, only the 180 height SNPs underwent drift and selection, in order to calibrate the number of generations for which selection should act in the second population. We allowed the simulations to proceed until the 180 height SNPs in the third population reached the 1.2% mean frequency difference observed in the original data. Once this mean frequency difference was met, selection was "turned off" in the second population. We then, if necessary, allowed drift to continue in each of the first two populations until the genome-wide F_{ST} between these two simulated data sets matched the F_{ST} for the observed data. The allele frequency data from these first two simulated populations were used in the analyses. By this procedure, each pair of simulated data sets is matched to the actual Northern- and Southern-European data by the allele frequency spectrum, by the average differentiation of the known height-associated SNPs and also by the overall F_{ST} between NEur and SEur.

We varied the input parameters over a range of s and N_e. Five replicate simulations were performed for each combination of input parameters. For each replicate, we then determined if a model incorporating drift plus selection or a model with drift alone better fit the data by calculating the LRT statistic, using either the top ~1,400 SNPs or the larger genome-wide data set of ~56,000 SNPs. We estimated the selective parameter s using the likelihood ratio approach as described in section 2. For each combination of input parameters, we report the results for the median of these five replicates (Supplementary Table 2). For all combinations of parameters

tested, the LRT p values were strongly significant (and comparable to those observed in the actual data) and estimated selective coefficients were extremely close to the input parameters used, thereby confirming both the validity and the power of our approach.

4 Derivation of the allele frequency difference expected due to weak selection

To calculate the expected allele frequency difference between two populations after selection for T generations, we begin with the frequency of an allele after one generation of selection, namely

$$p' = \frac{p^2 w_{11} + pqw_{12}}{p^2 w_{11} + 2pqw_{12} + q^2 w_{22}} \quad (1)$$

where p' is the frequency after one generation of selection, p is the frequency before selection, q is $1 - p$, and w_{11}, w_{12}, and w_{22}, are the selection pressures experienced by individuals homozygous for allele 1, heterozygous for the two alleles, and homozygous for allele 2, respectively. We assumed that allele 1 is under selection, thus the relative fitness for w_{11}, w_{12}, and w_{22} are 1+2w, 1+w, and 1, respectively, for some constant w (ref 17).

If the total effect of selection is small (as suggested by our small observed AF differences at height-associated SNPs), the difference in frequency after T generations between two populations, one of which is under selection, is approximately

$$\Delta AF_{Sel} \approx T \times [p' - p]$$

We can replace p' with equation 1 to get:

$$\Delta AF_{Sel} \approx T \times \left[\frac{p^2 w_{11} + pqw_{12}}{p^2 w_{11} + 2pqw_{12} + q^2 w_{22}} - p \right]$$

Substituting in the relative fitness for w_{11}, w_{12}, and w_{22}, we get:

$$\Delta AF_{Sel} \approx T \times \left[\frac{p^2(1+2w) + pq(1+w)}{p^2(1+2w) + 2pq(1+w) + q^2} - p \right]$$

After some algebra the expression simplifies to:

$$\Delta AF_{Sel} \approx T \times \left(\frac{wp^2 + wp + p}{1+2wp} - p \right) (2)$$

We use equation (2) to model the effects of selection under different models by setting w = s, w= s*β, or w= $s_1 + s_2$*β (see Section 2 above).

5 GIANT Consortium authors and affiliations

Lango Allen,Hana[1], Estrada,Karol[2,3,4], Lettre,Guillaume[5,6], Berndt,Sonja I.[7], Weedon,Michael N.[1], Rivadeneira,Fernando[2,3,4], Willer,Cristen J.[8], Jackson,Anne U.[8], Vedantam,Sailaja[9,10], Raychaudhuri,Soumya[11,12], Ferreira,Teresa[13], Wood,Andrew R.[1], Weyant,Robert J.[8], Segrè, Ayellet V.[11,14,15], Speliotes,Elizabeth K.[10,16], Wheeler,Eleanor[17], Soranzo,Nicole[17,18], Park,Ju-Hyun[7], Yang,Jian[19], Gudbjartsson,Daniel[20], Heard-Costa,Nancy L.[21], Randall,Joshua C.[13], Qi,Lu[22,23], Smith,Albert Vernon[24,25], Mägi,Reedik[13], Pastinen,Tomi[26,27,28], Liang,Liming[29], Heid,Iris M.[30,31], Luan,Jian'an[32], Thorleifsson,Gudmar[20], Winkler,Thomas W.[30], Goddard,Michael E.[33,34], Lo,Ken Sin[5], Palmer,Cameron[9,10], Workalemahu,Tsegaselassie[22], Aulchenko,Yurii S.[2,4], Johansson,Åsa[35,36], Zillikens,M.Carola[3], Feitosa,Mary F.[37], Esko,Tõnu[38,39,40], Johnson,Toby[41,42,43,44], Ketkar,Shamika[37], Kraft,Peter[45,46], Mangino,Massimo[18], Prokopenko,Inga[13,47], Absher,Devin[48] , Albrecht,Eva[31], Ernst,Florian[49], Glazer,Nicole L.[50], Hayward,Caroline[51], Hottenga,Jouke-Jan[52], Jacobs,Kevin B.[53], Knowles,Joshua W.[54], Kutalik,Zoltán[41,42], Monda,Keri L.[55], Polasek,Ozren[56,57], Preuss,Michael[58], Rayner,Nigel W.[13,47], Robertson,Neil R.[13,47], Steinthorsdottir,Valgerdur[20], Tyrer,Jonathan P.[59], Voight,Benjamin F.[11,14,15], Wiklund,Fredrik[60], Xu,Jianfeng[61], Zhao,Jing Hua[32], Nyholt,Dale R.[62], Pellikka,Niina[63,64], Perola,Markus[63,64], Perry,John R.B.[1], Surakka,Ida[63,64], Tammesoo,Mari-Liis[38], Altmaier, Elizabeth L.[9,10], Amin,Najaf[2], Aspelund,Thor[24,25], Bhangale,Tushar[65], Boucher,Gabrielle[5], Chasman,Daniel I.[66,67], Chen,Constance[68], Coin,Lachlan[69], Cooper,Matthew N.[70], Dixon,Anna L.[71], Gibson, Quince[72], Grundberg,Elin[17,26,27], Hao,Ke[73], Junttila, M. Juhani[74], Kaplan,Lee M.[16,67,75], Kettunen,Johannes[63,64], König,Inke R.[58], Kwan,Tony[26,27], Lawrence,Robert W.[70], Levinson,Douglas F.[76], Lorentzon,Mattias[77], McKnight,Barbara[78], Morris,Andrew P.[13], Müller,Martina[31,79,80], Ngwa,Julius Suh[81], Purcell,Shaun[14,82,83], Rafelt,Suzanne[84], Salem,Rany M.[9,10], Salvi,Erika[85,86], Sanna,Serena[87], Shi,Jianxin[7], Sovio,Ulla[69], Thompson,John R.[88,89], Turchin,Michael C.[9,10], Vandenput,Liesbeth[77], Verlaan,Dominique J.[26,27], Vitart,Veronique[51], White,Charles C.[81], Ziegler,Andreas[90], Almgren,Peter[91], Balmforth,Anthony J.[92], Campbell,Harry[93], Citterio,Lorena[94], De Grandi,Alessandro[95], Dominiczak,Anna[96], Duan,Jubao[97], Elliott,Paul[69], Elosua, Roberto[98], Eriksson,Johan

G.[99,100,101,102,103], Freimer,Nelson B.[104], Geus,Eco J.C.[52], Glorioso,Nicola[105], Haiqing,Shen[72], Hartikainen,Anna-Liisa[106], Havulinna,Aki S.[107], Hicks,Andrew A.[95], Hui,Jennie[70,108,109], Igl,Wilmar[35], Illig,Thomas[31], Jula,Antti[110], Kajantie,Eero[100], Kilpeläinen,Tuomas O.[32], Koiranen,Markku[111], Kolcic,Ivana[56], Koskinen,Seppo[107], Kovacs,Peter[112], Laitinen,Jaana[113], Liu,Jianjun[114], Lokki,Marja-Liisa[115], Marusic,Ana[116], Maschio,Andrea[87], Meitinger,Thomas[117,118], Mulas,Antonella[87], Paré,Guillaume[119], Parker,Alex N.[120], Peden,John F.[13,121], Petersmann,Astrid[122], Pichler,Irene[95], Pietiläinen,Kirsi H.[123,124], Pouta,Anneli[106,125], Ridderstråle,Martin[126], Rotter,Jerome I.[127], Sambrook,Jennifer G.[128,129], Sanders,Alan R.[97], Schmidt,Carsten Oliver[130], Sinisalo,Juha[131], Smit,Jan H.[132], Stringham,Heather M.[8], Walters,G.Bragi[20], Widen,Elisabeth[63], Wild,Sarah H.[93], Willemsen,Gonneke[52], Zagato,Laura[94], Zgaga,Lina[56], Zitting,Paavo[133], Alavere,Helene[38], Farrall,Martin[13,121,134], McArdle,Wendy L.[135], Nelis,Mari[38,39,40], Peters,Marjolein J.[3,4], Ripatti,Samuli[63,64], van Meurs,Joyce B.J.[2,3,4], Aben,Katja K.[136], Ardlie,Kristin G[11], Beckmann,Jacques S.[41,137], Beilby,John P.[108,109,138], Bergman,Richard N.[139], Bergmann,Sven[41,42], Collins,Francis S.[140], Cusi,Daniele[85], den Heijer,Martin[141], Eiriksdottir,Gudny[24], Gejman,Pablo V.[97], Hall,Alistair S.[92], Hamsten,Anders[142], Huikuri,Heikki V.[74,74], Iribarren,Carlos[143,144], Kähönen,Mika[145], Kaprio,Jaakko[63,123,146], Kathiresan,Sekar[11,14,147,148,149], Kiemeney,Lambertus[136,150,151], Kocher,Thomas[152], Launer,Lenore J.[153], Lehtimäki,Terho[154], Melander,Olle[126], Mosley Jr,Tom H.[155], Musk,Arthur W.[109,156], Nieminen,Markku S.[131,131], O'Donnell,Christopher J.[148,157], Ohlsson,Claes[77], Oostra,Ben[158], Palmer,Lyle J.[70,109], Raitakari,Olli[159], Ridker,Paul M.[66,67], Rioux,John D.[5,6], Rissanen,Aila[124], Rivolta,Carlo[41], Schunkert,Heribert[160], Shuldiner,Alan R.[72,161], Siscovick,David S.[162,163], Stumvoll,Michael[164,165], Tönjes,Anke[164,166], Tuomilehto,Jaakko[167,168,169], van Ommen,Gert-Jan[170], Viikari,Jorma[171], Heath,Andrew C.[172], Martin,Nicholas G.[173], Montgomery,Grant W.[174] , Province,Michael A.[37,175], Kayser,Manfred[176], Arnold,Alice M.[78,177], Atwood,Larry D.[21], Boerwinkle,Eric[178], Chanock,Stephen J.[7], Deloukas,Panos[17], Gieger,Christian[31], Grönberg,Henrik[60], Hall,Per[60], Hattersley,Andrew T.[1], Hengstenberg,Christian[179,180], Hoffman,Wolfgang[130], Lathrop,G.Mark[181], Salomaa,Veikko[107], Schreiber,Stefan[182], Uda,Manuela[87], Waterworth,Dawn[183], Wright,Alan F.[51], Assimes,Themistocles L.[54], Barroso,Inês[17,184], Hofman,Albert[2,4], Mohlke,Karen L.[185], Boomsma,Dorret I.[52], Caulfield,Mark J.[44], Cupples,L.Adrienne[81], Erdmann,Jeanette[160], Fox,Caroline S.[186], Gudnason,Vilmundur[24,25], Gyllensten,Ulf[35], Harris,Tamara B.[153], Hayes,Richard B.[187], Jarvelin,Marjo-Riitta[69,111,125,188], Mooser,Vincent[183], Munroe,Patricia B.[44], Ouwehand,Willem H.[17,128,129], Penninx,Brenda W.[132,189,190], Pramstaller,Peter P.[95,191,192], Quertermous,Thomas[54], Rudan,Igor[51,116] , Samani,Nilesh J.[84,88], Spector,Timothy D.[18], Völzke,Henry[130], Watkins, Hugh on behalf of Procardis Consortium[13,121], Wilson,James F.[93], Groop,Leif C.[91], Haritunians,Talin[127], Hu,Frank B.[22,23,45], Kaplan,Robert C.[193], Metspalu,Andres[38,39,40], North,Kari E.[55,194], Schlessinger,David[195], Wareham,Nicholas J.[32], Hunter,David J.[22,23,45], O'Connell,Jeffrey R.[72], Strachan,David P.[196], Wichmann,H.-Erich[31,80,197], Borecki,Ingrid B.[37,175], van Duijn,Cornelia M.[2,4], Schadt,Eric E.[198,199], Thorsteinsdottir,Unnur[20,200], Peltonen,Leena[17,63,64,82,201], Uitterlinden,André[2,3,4], Visscher,Peter M.[19], Chatterjee,Nilanjan[7], Loos,Ruth J.F.[32], Boehnke,Michael[8], McCarthy,Mark I.[13,47,202], Ingelsson,Erik[60], Lindgren,Cecilia M.[13,47], Abecasis,Gonçalo R.[8], Stefansson,Kari[20,200], Frayling,Timothy M.[1], Hirschhorn,Joel N.[9,10,203]

1. Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, EX1 2LU, UK
2. Department of Epidemiology, Erasmus MC, Rotterdam, 3015GE, The Netherlands
3. Department of Internal Medicine, Erasmus MC, Rotterdam, 3015GE, The Netherlands
4. Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA)

5. Montreal Heart Institute, Montreal, Quebec, H1T 1C8, Canada
6. Department of Medicine, Université de Montréal, Montreal, Quebec, H3T 1J4, Canada
7. Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892, USA
8. Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA
9. Divisions of Genetics and Endocrinology and Program in Genomics, Children's Hospital, Boston, Massachusetts 02115, USA
10. Metabolism Initiative and Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts 02142, USA
11. Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA
12. Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115 USA
13. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK
14. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
15. Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
16. Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
17. Wellcome Trust Sanger Institute, Hinxton, Cambridge, CB10 1SA, UK
18. Department of Twin Research and Genetic Epidemiology, King's College London, Lambeth Palace Rd, London, SE1 7EH, UK
19. Queensland Statistical Genetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
20. deCODE Genetics, 101 Reykjavik, Iceland
21. Department of Neurology, Boston University School of Medicine, Boston, Massachusetts 02118, USA
22. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA
23. Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA
24. Icelandic Heart Association, Kopavogur, Iceland
25. University of Iceland, Reykjavik, Iceland
26. McGill University and Genome Québec Innovation Centre, Montréal, Québec H3A 1A4, Canada.
27. Department of Human Genetics, McGill University Health Centre, McGill University, Montréal, Québec H3G 1A4, Canada
28. Department of Medical Genetics, McGill University Health Centre, McGill University, Montréal, Québec H3G 1A4, Canada
29. Departments of Epidemiology and Biostatistics, Harvard School of Public Health, Cambridge, Massachusetts 02138, USA
30. Regensburg University Medical Center, Department of Epidemiology and Preventive Medicine, 93053 Regensburg, Germany
31. Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany
32. MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK
33. University of Melbourne, Parkville 3010, Australia
34. Department of Primary Industries, Melbourne, Victoria 3001, Australia
35. Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, SE-75185 Uppsala, Sweden
36. Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, N-7489, Norway
37. Department of Genetics, Washington University School of Medicine, St Louis, Missouri 63110, USA
38. Estonian Genome Center, University of Tartu, Tartu 50410, Estonia
39. Estonian Biocenter, Tartu 51010, Estonia
40. Institute of Molecular and Cell Biology, University of Tartu, Tartu 51010, Estonia
41. Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland
42. Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland
43. Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK
44. Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK
45. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA
46. Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts 02115, USA
47. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, OX3 7LJ, UK
48. Hudson Alpha Institute for Biotechnology, Huntsville, Alabama 35806, USA
49. Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany
50. Cardiovascular Health Resarch Unit and Department of Medicine, University of Washington, Seattle, Washington 98101, USA
51. MRC Human Genetics Unit, Institute for Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU, Scotland, UK
52. Department of Biological Psychology, VU University Amsterdam, 1081 BT Amsterdam, The Netherlands
53. Core Genotyping Facility, SAIC-Frederick, Inc., NCI-Frederick, Frederick, Maryland 21702, USA
54. Department of Medicine, Stanford University School of Medicine, Stanford, California 94305, USA

55. Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514 USA
56. Andrija Stampar School of Public Health, Medical School, University of Zagreb, 10000 Zagreb, Croatia
57. Gen-Info Ltd, 10000 Zagreb, Croatia
58. Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik, 23562 Lübeck, Germany
59. Department of Oncology, University of Cambridge, Cambridge, CB1 8RN, UK
60. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden
61. Center for Human Genomics, Wake Forest University, Winston-Salem, North Carolina 27157, USA
62. Neurogenetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
63. Institute for Molecular Medicine Finland (FIMM), University of Helsinki, 00014, Helsinki, Finland
64. National Institute for Health and Welfare, Department of Chronic Disease Prevention, Unit of Public Health Genomics, 00014, Helsinki, Finland
65. Department of Genome Sciences, University of Washington, Seattle, 98195 Washington, USA
66. Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts 02215, USA
67. Harvard Medical School, Boston, Massachusetts 02115, USA
68. Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA
69. Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College London, London, W2 1PG , UK
70. Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, Western Australia 6009, Australia
71. Royal National Hospital for Rheumatic Diseases and University of Bath, Bath, BA1 1RL, UK
72. Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA
73. Genetics Department, Rosetta Inpharmatics, a Wholly Owned Subsidiary of Merck & Co. Inc., Seattle, Washington 98109, USA
74. Department of Internal Medicine, University of Oulu, 90014 Oulu, Finland
75. MGH Weight Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
76. Stanford University School of Medicine, Stanford, California 93405, USA
77. Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden
78. Departments of Biostatistics, University of Washington, Seattle, Washington 98195, USA
79. Ludwig-Maximilians-University, Department of Medicine I, University Hospital Grosshadern, 81377 Munich, Germany
80. Ludwig-Maximilians-Universität, Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, 81377 Munich, Germany
81. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA
82. The Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02142, USA
83. Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115, USA
84. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK
85. University of Milan, Department of Medicine, Surgery and Dentistry, 20139 Milano, Italy
86. KOS Genetic Srl, 20123 Milan, Italy
87. Istituto di Neurogenetica e Neurofarmacologia del CNR, Monserrato, 09042, Cagliari, Italy
88. Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK
89. Department of Health Sciences, University of Leicester, University Road, Leicester, LE1 7RH, UK
90. Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik, 23562 Lübeck, Germany
91. Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden
92. Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds LS2 9JT, UK
93. Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland
94. University Vita-Salute San Raffaele, Division of Nephrology and Dialysis, 20132 Milan, Italy
95. Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano/Bozen, 39100, Italy. Affiliated Institute of the University of Lübeck, Lübeck, Germany.
96. British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, G12 8TA, UK
97. Northshore University Healthsystem, Evanston, Ilinois 60201, USA
98. Cardiovascular Epidemiology and Genetics, Institut Municipal D'investigacio Medica and CIBER Epidemiología y Salud Pública, Barcelona, Spain
99. Department of General Practice and Primary health Care, University of Helsinki, Helsinki, Finland
100. National Institute for Health and Welfare, 00271 Helsinki, Finland
101. Helsinki University Central Hospital, Unit of General Practice, 00280 Helsinki, Finland
102. Folkhalsan Research Centre, 00250 Helsinki, Finland
103. Vasa Central Hospital, 65130 Vasa, Finland
104. Center for Neurobehavioral Genetics, University of California, Los Angeles, California 90095, USA
105. Hypertension and Cardiovascular Prevention Center, University of Sassari, 07100 Sassari, Italy
106. Department of Clinical Sciences/Obstetrics and Gynecology, University of Oulu, 90014 Oulu, Finland

107. National Institute for Health and Welfare, Department of Chronic Disease Prevention, Chronic Disease Epidemiology and Prevention Unit, 00014, Helsinki, Finland
108. PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands, Western Australia 6009, Australia
109. Busselton Population Medical Research Foundation Inc., Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia
110. National Institute for Health and Welfare, Department of Chronic Disease Prevention, Population Studies Unit, 20720 Turku, Finland
111. Institute of Health Sciences, University of Oulu, 90014 Oulu, Finland
112. Interdisciplinary Centre for Clinical Research, University of Leipzig, 04103 Leipzig, Germany
113. Finnish Institute of Occupational Health, 90220 Oulu, Finland
114. Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore
115. Transplantation Laboratory, Haartman Institute, University of Helsinki, 00014, Helsinki, Finland
116. Croatian Centre for Global Health, School of Medicine, University of Split, Split 21000, Croatia
117. Institute of Human Genetics, Klinikum rechts der Isar der Technischen Universität München, 81675 Munich, Germany
118. Institute of Human Genetics, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany
119. Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario L8N3Z5, Canada
120. Amgen, Cambridge, Massachusetts 02139, USA
121. Department of Cardiovascular Medicine, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU
122. Institut für Klinische Chemie und Laboratoriumsmedizin, Universität Greifswald, 17475 Greifswald, Germany
123. Finnish Twin Cohort Study, Department of Public Health, University of Helsinki, 00014, Helsinki, Finland
124. Obesity Research unit, Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland
125. National Institute for Health and Welfare, 90101 Oulu, Finland
126. Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden
127. Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA
128. Department of Haematology, University of Cambridge, Cambridge CB2 0PT, UK
129. NHS Blood and Transplant, Cambridge Centre, Cambridge, CB2 0PT, UK
130. Institut für Community Medicine, 17489 Greifswald, Germany
131. Division of Cardiology, Cardiovascular Laboratory, Helsinki University Central Hospital, 00029 Helsinki, Finland
132. Department of Psychiatry/EMGO Institute, VU University Medical Center, 1081 BT Amsterdam, The Netherlands
133. Department of Psychiatrics, Lapland Central Hospital, 96101 Rovaniemi, Finland
134. Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Oxford, OX3 7BN, UK
135. Avon Longitudinal Study of Parents and Children (ALSPAC) Laboratory, Department of Social Medicine, University of Bristol, Bristol, BS8 2BN, UK
136. Comprehensive Cancer Center East, 6501 BG Nijmegen, The Netherlands
137. Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois (CHUV) University Hospital, 1011 Lausanne, Switzerland
138. School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia 6009,Australia
139. Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA
140. National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
141. Department of Endocrinology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands
142. Atherosclerosis Research Unit, Department of Medicine, Solna,Karolinska Institutet, Karolinska University Hospital, 171 76 Stockholm, Sweden
143. Division of Research, Kaiser Permanente Northern California, Oakland, California 94612, USA
144. Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California 94107, USA
145. Department of Clinical Physiology, University of Tampere and Tampere University Hospital, 33520 Tampere, Finland;
146. National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Unit for Child and Adolescent Mental Health, 00271 Helsinki, Finland
147. Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
148. Framingham Heart Study of the National, Heart, Lung, and Blood Institute and Boston University, Framingham, Massachusetts 01702, USA
149. Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA
150. Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands
151. Department of Urology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands
152. Zentrum für Zahn-, Mund- und Kieferheilkunde, 17489 Greifswald, Germany
153. Laboratory of Epidemiology, Demography, Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA
154. Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, 33520 Tampere, Finland

155. Department of Medicine, Division of Geriatrics, University of Mississippi Medical Center, Jackson, Mississippi 39216, USA
156. School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia 6009, Australia
157. National, Lung, and Blood Institute, National Institutes of Health, Framingham, Massachusetts 01702, USA
158. Department of Clinical Genetics, Erasmus MC, Rotterdam, 3015GE, The Netherlands
159. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and the Department of Clinical Physiology, Turku University Hospital, 20520 Turku, Finland
160. Universität zu Lübeck, Medizinische Klinik II, 23562 Lübeck, Germany
161. Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, Maryland 21201, USA
162. Cardiovascular Health Research Unit, University of Washington, Seattle, Washington 98101, USA
163. Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington 98195, USA
164. Department of Medicine, University of Leipzig, 04103 Leipzig, Germany
165. LIFE Study Centre, University of Leipzig, Leipzig, Germany
166. Coordination Centre for Clinical Trials, University of Leipzig, Härtelstr. 16-18, 04103 Leipzig, Germany
167. National Institute for Health and Welfare, Diabetes Prevention Unit, 00271 Helsinki, Finland
168. Hjelt Institute, Department of Public Health, University of Helsinki, 00014 Helsinki, Finland
169. South Ostrobothnia Central Hospital, 60220 Seinajoki, Finland
170. Department of Human Genetics and Center of Medical Systems Biology, Leiden University Medical Center, 2333 ZC Leiden, the Netherlands
171. Department of Medicine, University of Turku and Turku University Hospital, 20520 Turku, Finland
172. Department of Psychiatry and Midwest Alcoholism Research Center, Washington University School of Medicine, St Louis, Missouri 63108, USA
173. Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
174. Molecular Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
175. Division of Biostatistics,Washington University School of Medicine,St.Louis, Missouri 63110, USA
176. Department of Forensic Molecular Biology, Erasmus MC, Rotterdam, 3015GE, The Netherlands
177. Collaborative Health Studies Coordinating Center, Seattle, Washington 98115, USA
178. Human Genetics Center and Institute of Molecular Medicine and Division of Epidemiology, University of Texas Health Science Center, Houston, Texas 77030, USA
179. Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, 93053 Regensburg, Germany
180. Regensburg University Medical Center, Innere Medizin II, 93053 Regensburg, Germany
181. Centre National de Genotypage, Evry, Paris 91057, France
182. Christian-Albrechts-University, University Hospital Schleswig-Holstein, Institute for Clinical Molecular Biology and Department of Internal Medicine I, Schittenhelmstrasse 12, 24105 Kiel
183. Genetics Division, GlaxoSmithKline, King of Prussia, Pennsylvania 19406, USA
184. University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital, CB2 OQQ, Cambridge, UK
185. Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA
186. Division of Intramural Research, National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, Massachusetts 01702, USA
187. New York University Medical Center, New York, New York 10016, USA
188. Biocenter Oulu, University of Oulu, 90014 Oulu, Finland
189. Department of Psychiatry, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands
190. Department of Psychiatry, University Medical Centre Groningen, 9713 GZ Groningen, The Netherlands
191. Department of Neurology, General Central Hospital, Bolzano, Italy
192. Department of Neurology, University of Lübeck, Lübeck, Germany.
193. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York 10461, USA
194. Carolina Center for Genome Sciences, School of Public Health, University of North Carolina Chapel Hill, Chapel Hill, North Carolina 27514, USA
195. Laboratory of Genetics, National Institute on Aging, Baltimore, Maryland 21224, USA
196. Division of Community Health Sciences, St George's, University of London, London, SW17 0RE, UK
197. Klinikum Grosshadern, 81377 Munich, Germany
198. Pacific Biosciences, Menlo Park, California 94025, USA
199. Sage Bionetworks, Seattle, Washington 98109, USA
200. Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland
201. Department of Medical Genetics, University of Helsinki, 00014 Helsinki, Finland
202. NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LJ, UK
203. Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA

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