Supplementary Table 1. Study-specific summary statistics results and meta-analysis results for SNPs rs12689384 and rs2294956

Study	rs12689384								rs2294956							
	EA	EAF	N	OR	OR_95L	OR_95U	P	Imputed	EA	EAF	N	OR	OR_95L	OR_95U	P	Imputed
WTCCC1 cases - HT	G	0.858	1988	1.519	1.270	1.816	8.24E-07	yes	T	0.8578	1988	1.521	1.272	1.818	8.24E-07	yes
WTCCC1 cases - T1D	G	0.859	1988	1.395	1.165	1.671	0.00035	yes	T	0.8587	1988	1.399	1.168	1.675	0.00033	yes
WTCCC1 cases - CD	G	0.861	1976	1.304	1.087	1.564	0.00145	yes	T	0.8609	1976	1.308	1.091	1.568	0.00135	yes
WTCCC1 cases - BD	G	0.859	1984	1.287	1.074	1.543	0.00202	yes	T	0.859	1984	1.288	1.075	1.544	0.00201	yes
WTCCC1 cases - T2D	G	0.855	1966	1.315	1.094	1.581	0.00676	yes	T	0.8551	1966	1.317	1.095	1.583	0.00670	yes
WTCCC1 cases - CAD	G	0.845	1978	1.413	1.121	1.781	0.01641	yes	T	0.8456	1978	1.415	1.122	1.784	0.01617	yes
WTCCC2 UKBS controls	G	0.90251	2488	1.136	0.942	1.370	0.276	yes	T	0.9031	2477	1.128	0.934	1.361	0.310	yes
WTCCC2 58BC controls	G	0.90621	2699	0.915	0.762	1.099	0.434	yes	T	0.9058	2691	0.916	0.763	1.100	0.444	yes
SHIP	A	0.1178	4080	1.058	0.894	1.251	0.512	yes	C	0.1153	4048	1.037	0.876	1.228	0.675	yes
ARIC	A	0.1009	9121	0.916	0.815	1.029	0.140	no	na	na	na	na	na	na	na	na
KORA S4	A	0.0973	1808	0.825	0.638	1.067	0.143	no	na	na	na	na	na	na	na	na
GerMIFS II	A	0.1064	1183	0.880	0.618	1.252	0.476	no	na	na	na	na	na	na	na	na
AGES	na	na	na	na	na	na	na	na	C	0.0895	3219	0.843	0.685	1.037	0.106	no
PREVEND	na	na	na	na	na	na	na	na	C	0.1093	3868	1.134	0.947	1.359	0.170	no
QIMR	na	na	na	na	na	na	na	na	C	0.105	5849	1.111	0.953	1.297	0.180	no
INGI-VB	na	na	na	na	na	na	na	na	C	0.102	711	1.354	0.836	2.191	0.216	no
BLSA	na	na	na	na	na	na	na	na	C	0.1036	848	0.838	0.618	1.136	0.255	no
NFBC1966	na	na	na	na	na	na	na	na	G	0.0949	5363	0.926	0.792	1.082	0.333	no
FINRISK	na	na	na	na	na	na	na	na	G	0.1106	4122	0.927	0.786	1.092	0.362	no
FUSION-T2D-cases	na	na	na	na	na	na	na	na	C	0.0949	1160	0.871	0.630	1.206	0.406	no
CROATIA-Korcula	na	na	na	na	na	na	na	na	G	0.1213	944	1.175	0.795	1.736	0.418	no
CROATIA-Vis	na	na	na	na	na	na	na	na	G	0.105	991	0.872	0.613	1.241	0.446	no
NTR2	na	na	na	na	na	na	na	na	C	0.101	1173	0.901	0.642	1.263	0.545	no
FUSION-controls	na	na	na	na	na	na	na	na	C	0.1003	1173	0.914	0.661	1.264	0.586	no
HBCS	na	na	na	na	na	na	na	na	G	0.11	1620	1.072	0.807	1.425	0.630	no
EGCUT	na	na	na	na	na	na	na	na	C	0.1255	2430	0.952	0.774	1.170	0.639	no
ECHRS-Spain	na	na	na	na	na	na	na	na	C	0.0864	366	0.888	0.519	1.520	0.665	no
H2000	na	na	na	na	na	na	na	na	G	0.11	2118	1.048	0.824	1.331	0.704	no
InCHIANTI	na	na	na	na	na	na	na	na	C	0.1184	1210	1.055	0.771	1.444	0.738	no
TwinsUK	na	na	na	na	na	na	na	na	A	0.8997	3576	0.940	0.648	1.362	0.743	no
CROATIA-Split	na	na	na	na	na	na	na	na	G	0.1136	499	0.922	0.568	1.497	0.743	no
ORCADES	na	na	na	na	na	na	na	na	G	0.0845	889	0.944	0.626	1.423	0.783	no
RAINE	na	na	na	na	na	na	na	na	G	0.1046	1494	1.010	0.757	1.346	0.948	no
YFS	na	na	na	na	na	na	na	na	G	0.1051	2443	0.999	0.796	1.255	0.994	no
Meta-analysis (GC corrected)	**G**	**0.8825**	**33259**	**1.17896**	**1.112**	**1.250**	**3.27E-08**	**na**	**T**	**0.8886**	**67162**	**1.08546**	**1.040**	**1.133**	**1.99E-04**	**na**

EA - effect allele; EAF - effect allele frequency; N - total number of samples; OR - odds ratio: OR_95L and OR_95U - 95% confidence intervals; P - p-value; GC-genomic control

Supplementary Table 2: The characteristics of samples

					Women	Men	
Study (short name)	Study (Full name)	No women (cases)	No men (controls)	Total	Mean age, years, (stdev)	Mean age, years, (stdev)	PMID number/Reference
AGES	Age, Gene/Environment Susceptibility (AGES Reykjavik) Study	1867	1352	3219	76.34 (5.55)	76.52 (5.32)	17351290
ARCTIC-cases	Assessment of Risk for Colorectal Cancer Tumours in Canada	673	511	1184	63.2 (8.38)	62.4 (8.46)	17618283
ARCTIC-controls	Assessment of Risk for Colorectal Cancer Tumours in Canada	513	665	1178	62.6 (9.5)	64.3 (7.9)	17618283
ARIC	The Atherosclerosis Risk in Communities Study	4938	4407	9345	53.94 (5.67)	54.67 (5.69)	2646917
BLSA	Baltimore Longitudinal Study of Aging	386	462	848	68.01 (17.8)	72.89 (15.32)	/
CARLANTINO	INGI-Carlantino	398	278	676	45.09 (20.43)	44.52 (20.09)	21248747, 19067108, 21102462
CoLaus	Cohorte Lausannoise	2875	2560	5435	52.94 (10.71)	52.94 (10.75)	18366642
CROATIA-Korcula	CROATIA-Korcula	573	325	898	55.54 (13.71)	57.55 (14.27)	19260141
CROATIA-Split	CROATIA-Split	286	213	499	49.88 (13.94)	47.92 (15.51)	19260138
CROATIA-Vis	CROATIA-Vis	535	388	923	56.72 (15.99)	55.88 (14.9)	18327257
ECHRS-Spain	European Community Respiratory Health Survey, Spain	220	205	425	41.6 (6.73)	41 (7.22)	18385169
EGCUT	Estonian Genome Centre, University of Tartu	1251	1193	2444	43.6 (14.8)	43.6 (15.1)	19424496
EPIC-Obesity	The European Prospective Investigation of Cancer	1931	1621	3552	58.76 (8.92)	59.85 (8.98)	10466767, 18454148
FENLAND	The Fenland Study	787	615	1402	45.35 (7.19)	44.45 (7.36)	19079261
FINRISK	Finrisk and Corogene	1567	2555	4122	62.79 (13.48)	60.33 (12.90)	19820697
FUSION-controls	Finland-United States Investigation of NIDDM Genetics NGT controls	600	573	1173	63.72 (7.27)	63.41 (7.61)	17463248
FUSION-T2D-cases	Finland-United States Investigation of NIDDM Genetics T2D cases	507	653	1160	63.98 (7.87)	62.09 (7.35)	17463248
FVG	INGI-FVG	806	548	1354	48.75 (19.53)	47.77 (19.08)	18719631
GerMIFS I	German Myocardial Infarction Family Study I	309	641	950	52.55 (8.37)	48.89 (7.43)	17634449
GerMIFS II	German Myocardial Infarction Family Study II	235	948	1183	52.9 (7.74)	50.94 (7.51)	19198612
GerMIFS III	German Myocardial Infarction Family Study III	233	919	1152	60.78 (8.39)	58.1 (8.74)	21088011
H2000	Health 2000 Gemets substudy	1084	1034	2118	52.2 (11.54)	49.3 (10.35)	http://www.terveys2000.fi/indexe.html
HBCS	Helsinki Birth Cohort Study	916	704	1620	61.55 (3.03)	61.4 (2.75)	11312225
InCHIANTI	Invecchiare nel Chianti	670	540	1210	69.1 (15.6)	67.2 (15.4)	11129752, 18464913
INGI-VB	INGI-Val Borbera	413	298	711	53.7 (17.4)	56.2 (16.9)	19847309
KORA S3	Cooperative Health Research in the Region of Augsburg	831	813	1644	52.19 (10.09)	53.09 (10.08)	16032514
KORA S4	Cooperative Health Research in the Region of Augsburg	930	884	1814	53.52 (8.82)	54.10 (8.94)	16032514
NBS	Nijmegen Biomedical Study	926	906	1832	56.7 (10.8)	66.3 (7.0)	16254196
NESDA+NTR1	Netherlands Study of Depression and Anxiety	2324	1216	3540	42.6 (13.3)	46.1 (13.4)	18197199

NFBC1966	Northern Finland Birth Cohort 1966	2777	2587	5364	31 (0)	31 (0)	4911003
NTR2	Netherlands Twins Register Cohort	713	460	1173	47.5 (13.8)	50.7 (14.2)	18197199
ORCADES	Orkney Complex Disease Study	485	404	889	52.71 (15.71)	54.43 (15.73)	18760389
PREVEND	Prevention of Renal and Vascular End-stage Disease	1890	1978	3868	48.16 (12)	50.96 (12.73)	12356629
QIMR	Queensland Institute of Medical Research, Brisbane	3346	2536	5882	55.87 (16.65)	54.00 (16.91)	19896111
RAINE	Western Australian Pregnancy (Raine) Cohort	565	633	1198	17.06 (0.25)	17.01 (0.21)	8105165, 9224128, 8855394
RSI	Rotterdam Study I	3547	2427	5974	70.32 (9.60)	68.13 (8.16)	/
RSII	Rotterdam Study II	1156	973	2129	65.65 (8.86)	64.68 (7.82)	/
RSIII	Rotterdam Study III	1138	888	2026	57.28 (7.50)	56.95 (6.81)	/
SHIP	Study of Health in Pomerania	2072	2009	4081	48.61 (16.04)	50.89 (16.43)	20167617
SORBS	Sorbs	536	371	907	47.99 (15.94)	48.07 (16.71)	19729412; 19584900
TwinsUK	TwinsUK	2299	348	2647	58.31 (14.16)	56.61 (14.73)	17254428
WTCCC1 cases - BD	Wellcome Trust Case Control Consortium 1 for Bipolar Disorder	1247	751	1998	NA	NA	17554300
WTCCC1 cases - CAD	Wellcome Trust Case Control Consortium 1 for Coronary Artery Disease	399	1527	1926	NA	NA	17634449
WTCCC1 cases - CD	Wellcome Trust Case Control Consortium 1 for Crohn's Disease	1068	680	1748	NA	NA	17554261
WTCCC1 cases - HT	Wellcome Trust Case Control Consortium 1 for Hypertension	1177	775	1952	NA	NA	17554300
WTCCC1 cases - RA	Wellcome Trust Case Control Consortium 1 for Rheumatoid Arthritis	1390	470	1860	NA	NA	17982455
WTCCC1 cases - T1D	Wellcome Trust Case Control Consortium 1 for Type 1 Diabetes	985	1015	2000	NA	NA	18004301
WTCCC1 cases - T2D	Wellcome Trust Case Control Consortium 1 for Type 2 Diabetes	837	1162	1999	NA	NA	17463249
WTCCC2 58BC controls	Wellcome Trust Case Control Consortium 2 58 Birth Cohort	1306	1393	2699	NA	NA	/
WTCCC2 UKBS controls	Wellcome Trust Case Control Consortium 2 UK Blood Donors	1257	1231	2488	NA	NA	/
YFS	Young Finns Study	1320	1124	2444	37.57 (5.01)	37.55 (5.06)	18263651
Total		61094	53769	114863			

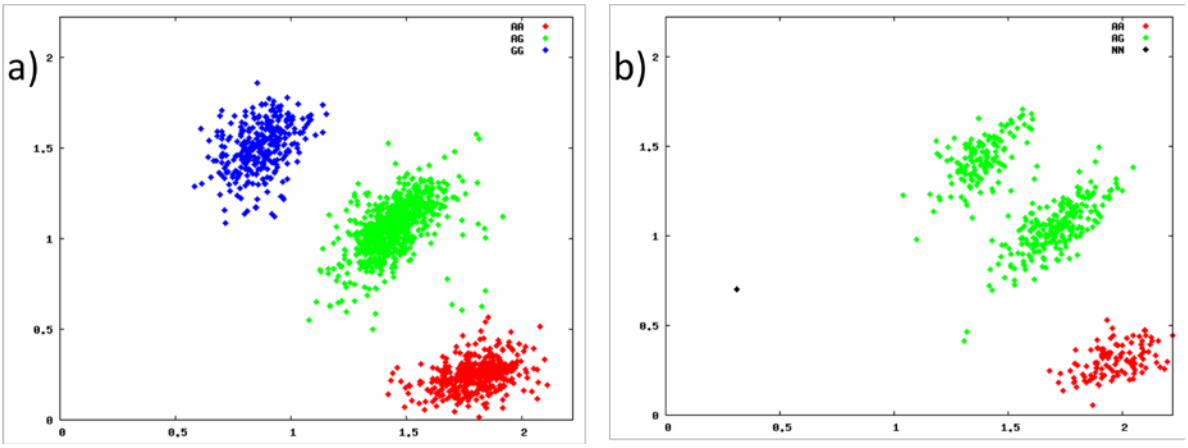
Supplementary Table 3. Study-specific information on genotyping platforms, imputation methods and QC metrics

		SNP QC metrics		Autosomal SNPs		Chromosome X SNPs		
Study (short name)	Genotyping platform	Call rate threshold (%)	HWE threshold (p-value)	Imputation /Analysis software	Analysed SNPs (after QC)	Imputation /Analysis software	Analysed pseudoautosomal SNPs (after QC)	Analysed non-pseudoautosomal SNPs (after QC)
AGES	Illumina HumanHapCNV370	97	< 1x10-6	MACH/ProbABEL	2133550	na/Plink	13	9061
ARCTIC-cases	Affymetrix 100k, 500k	90	< 1x10-5	Impute/SNPTEST	2116241	na/Plink	140	8516
ARCTIC-controls	Affymetrix 100k, 500k	90	< 1x10-5	Impute/SNPTEST	2128717	na/Plink	143	8551
ARIC	Affymetrix 6.0	97	< 1x10-6	MACH/ProbABEL	2102487	na/SAS-Plink	269	22620
BLSA	Illumina HUmanHap550K	99	< 1x10-4	MACH/MACH2 DAT	2019734	na/Plink	13	11865
CARLANTINO	Illumina HumanHapCNV370	90	0.05	MACH/GenABEL	2148522	na	na	na
CoLaus	Affymetrix 500K	70	< 1x10-7	Impute/Plink	2033730	na/Matlab	124	548
CROATIA-Korcula	Illumina HumanHapCNV370	98	< 1x10-6	MACH/ProbABEL	2139678	na/GenABEL-Plink	14	8799
CROATIA-Split	Illumina HumanHapCNV370	98	< 1x10-6	MACH/ProbABEL	2152695	na/GenABEL-Plink	23	8903
CROATIA-Vis	Illumina HumanHap300v1	98	< 1x10-6	MACH/ProbABEL	2143665	na/GenABEL-Plink	2	8293
ECHRS-Spain	Illumina 610-Quad	95	< 1x10-4	Plink/Plink	2008948	Plink/Plink	53	52855
EGCUT	Illumina HumanHapCNV370 & OmniExpress	95	< 1x10-6	Impute/SNPTEST	2067416	na/Plink	16	8729
EPIC-Obesity	Affymetrix 500K (Nsp+Sty)	90	< 1x10-6	Impute/SNPTEST	2067292	Impute/SNPTEST	3	30605
FENLAND	Affymetrix 5.0	90	< 1x10-6	Impute/SNPTEST	2040630	na/Plink	113	6731
FINRISK	Illumina 670-Quad	95	< 1x10-6	MACH/ProbABEL	2152121	na/Plink	29	12321
FUSION-controls	Illumina HumanHap300v1	90	< 1x10-6	MACH/MACH2 DAT	2099913	na/Plink	2	8458
FUSION-T2D-cases	Illumina HumanHap300v1	90	< 1x10-6	MACH/MACH2 DAT	2100299	na/Plink	2	8463
FVG	Illumina HumanHapCNV370	95	0.05	MACH/GenABEL	2178625	na/Plink	na	3859
GerMIFS I	Affymetrix NSP 250k, Affymetrix STY 250k	98	< 1x10-4	MACH/SNPTEST	493926	na/Plink	113	6709
GerMIFS II	Affymetrix 6.0	98	< 1x10-4	MACH/SNPTEST	1495040	na/Plink	275	23219
GerMIFS III	Affymetrix 5.0	98	< 1x10-4	MACH/SNPTEST	1165895	na/Plink	96	6803
H2000	Illumina 670-Quad	95	< 1x10-6	MACH/ProbABEL	2149493	na/Plink	30	12320
HBCS	Illumina 670-Quad	95	< 1x10-6	MACH/ProbABEL	2152013	na/Plink	12	11558
InCHIANTI	Illumina HumanHap550K	98	< 1x10-4	MACH/MACH2 DAT	2172799	na/Plink	na	10328
INGI-VB	Illumina HumanHapCNV370	90	< 1x10-4	MACH/PLINK	2128783	na/Plink	16	8081
KORA S3	Affymetrix 500K	none	none	Impute/SNPTEST	2086253	na/Plink	129	6957
KORA S4	Affymetrix 6.0	none	none	Impute/SNPTEST	2228028	na/Plink	281	22508
NBS	Illumina HumanHapCNV370	96	< 1x10-6	Impute/SNPTEST	2078620	na	na	na

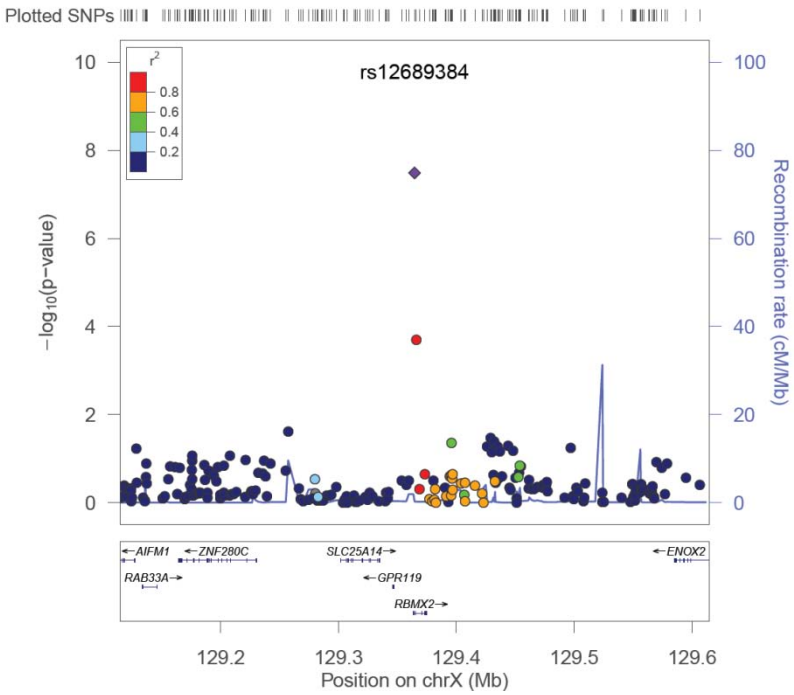
NESDA+NTR1	Affymetrix Perlegen 600K	95	none	Impute/SNPTEST	2157997	na/Plink	68	7608
NFBC1966	Illumina HumanHapCNV370	95	< 1x10-6	MACH/ProbABEL	2129175	na/Plink	16	9278
NTR2	Illumina Human660W-Quad	95	< 1x10-5	Impute/SNPTEST	2237592	na/Plink	na	11476
ORCADES	Illumina HumanHap300/HumanHapCNV370	98	< 1x10-6	MACH/ProbABEL	2137309	na/GenABEL-Plink	1	7699
PREVEND	HumanCytoSNP-12 BeadChip	98	< 1x10-5	Beagle/SNPTEST	1807142	na/Plink	476	8943
QIMR	Illumina	95	< 1x10-6	MACH/Plink	2133761	MaCH-minimac/Plink	1	31138
RAINE	Illumina Human660W-Quad	95	< 1x10-6	MACH/MACH2 DAT	2182062	na/Plink	13	11547
RSI	Illumina HumanHap550K	97.5	< 1x10-6	MACH/MACH2 DAT	2165420	na	na	na
RSII	Illumina HumanHap550K	97.5	< 1x10-6	MACH/MACH2 DAT	2163713	na	na	na
RSIII	Illumina HumanHap550K	97.5	< 1x10-6	MACH/MACH2 DAT	2164026	na	na	na
SHIP	Affymetrix 6.0	NA	NA	Impute/SNPTEST	2212837	BIMBAM/SNPTEST	52	41825
SORBS	Affymetrix 5.0/Affymetrix 6.0	95	< 1x10-4	Impute/SNPTEST	2066041	na/Plink	na	6901
TwinsUK	Illumina 610-Quad	95	< 1x10-6	Impute/SNPTEST	2168114	na/SNPTEST-Plink	36	12389
WTCCC1 cases - BD	Affymetrix 500K	95	< 5.7*10-7	Impute/SNPTEST	2098006	Impute/SNPTEST	448	47695
WTCCC1 cases - CAD	Affymetrix 500K	98	< 5.7*10-7	Impute/SNPTEST	2094737	Impute/SNPTEST	454	51694
WTCCC1 cases - CD	Affymetrix 500K	95	< 5.7*10-7	Impute/SNPTEST	2099887	Impute/SNPTEST	456	47874
WTCCC1 cases - HT	Affymetrix 500K	95	< 5.7*10-7	Impute/SNPTEST	2094644	Impute/SNPTEST	465	47634
WTCCC1 cases - RA	Affymetrix 500K	95	< 5.7*10-7	Impute/SNPTEST	2095114	Impute/SNPTEST	466	46691
WTCCC1 cases - T1D	Affymetrix 500K	99	0.004	Impute/SNPTEST	2097814	Impute/SNPTEST	452	48943
WTCCC1 cases - T2D	Affymetrix 500K	95	< 1x10-4	Impute/SNPTEST	2095993	Impute/SNPTEST	461	49571
WTCCC2 58BC controls	Illumina HumanHap 1M Duo	95	< 1x10-4	Impute/SNPTEST	2226640	Impute/SNPTEST	429	56833
WTCCC2 UKBS controls	Illumina HumanHap 1M Duo	95	< 1x10-4	Impute/SNPTEST	2226144	Impute/SNPTEST	420	56766
YFS	Illumina 670-Quad	95	< 1x10-6	MACH/ProbABEL	2146320	na/Plink	12	11591

Supplementary Table 4. Values of the demographic model parameters for time and effective population size

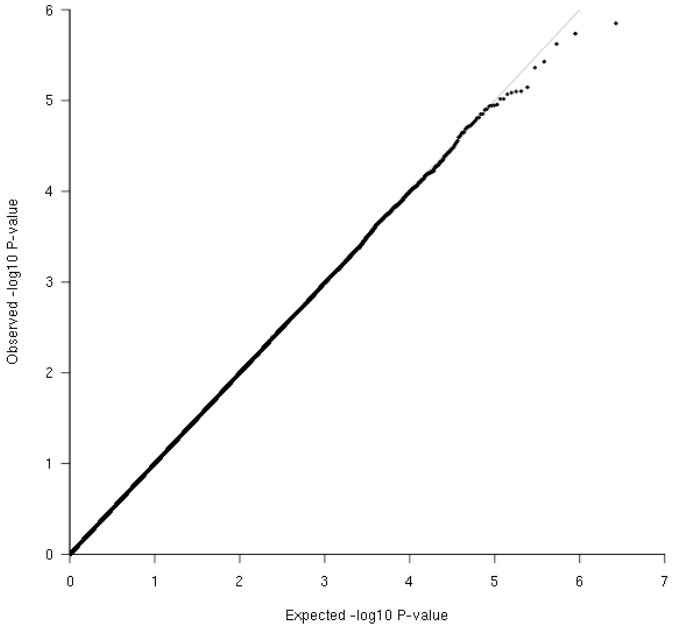
Time (generations ago)	Effective population size	Event
0	1,100,000	Post-agricultural expansion
350	7,700	Recovering European population size
1971	717	European bottleneck
2000	7,700	Out of Africa population size
3429	400	Out of Africa bottleneck
3500	24,000	Ancestral African population size
17000	12,500	Ancestral human population size



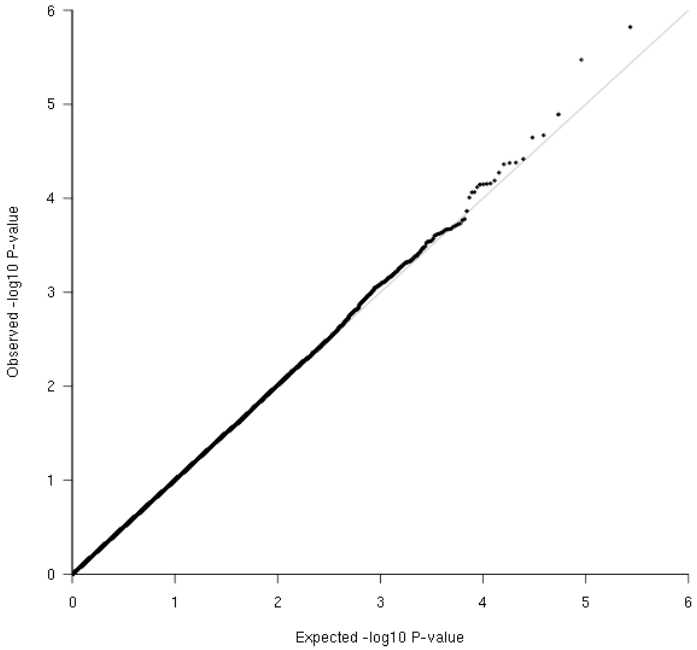
Supplementary Figure 1. An example of poor clustering (at SNP rs705736) in (a) women and (b) men, indicating genotyping error and leading to a false positive signal.



Supplementary Figure 2. Regional association plot of a non-pseudautosomal variant rs12689384. Association results (-log10 p value) are plotted against genomic position (NCBI build 36). The index SNP is denoted by a purple diamond and the circles represent association results of other SNPs from this region. The correlation coefficients (r^2) between index and each other SNP are estimated using the CEU HapMap II panel and are reflected by the colour of each circle. Estimated recombination rates are plotted in light blue. The region shown in the plot extends 250kb upstream and downstream of the index SNP. Regional association plot was plotted using LocusZoom (http://csg.sph.umich.edu/locuszoom/).

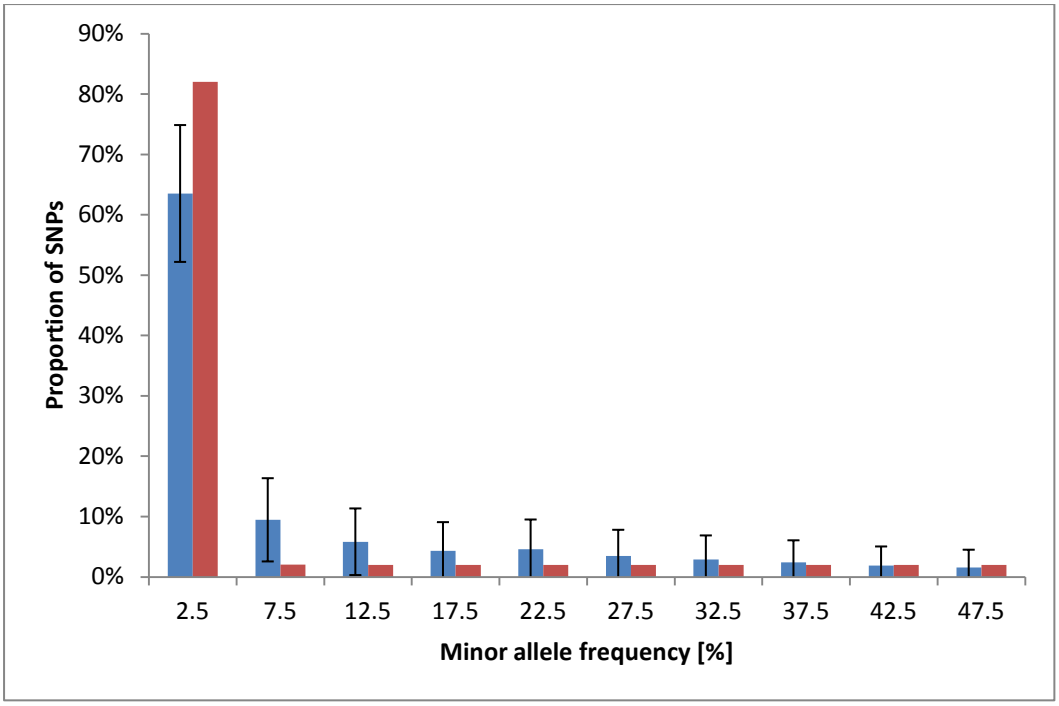


a) Common variants



b) Low frequency variants

Supplementary Figure 3. QQ plots for simulated variants: a) common (MAF>0.05) and b) low frequency (MAF 0.01-0.05)



Supplementary Figure 4. Minor allele frequency spectrum of the simulated data (red) compared with the experimental data (blue) from exome sequencing of individuals (2n=60) from the European (CEU) population in the 1000 Genomes Pilot 3 project. Ninety-nine percent confidence intervals obtained by re-sampling of individuals. Midpoint value for each frequency bin is reported.

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