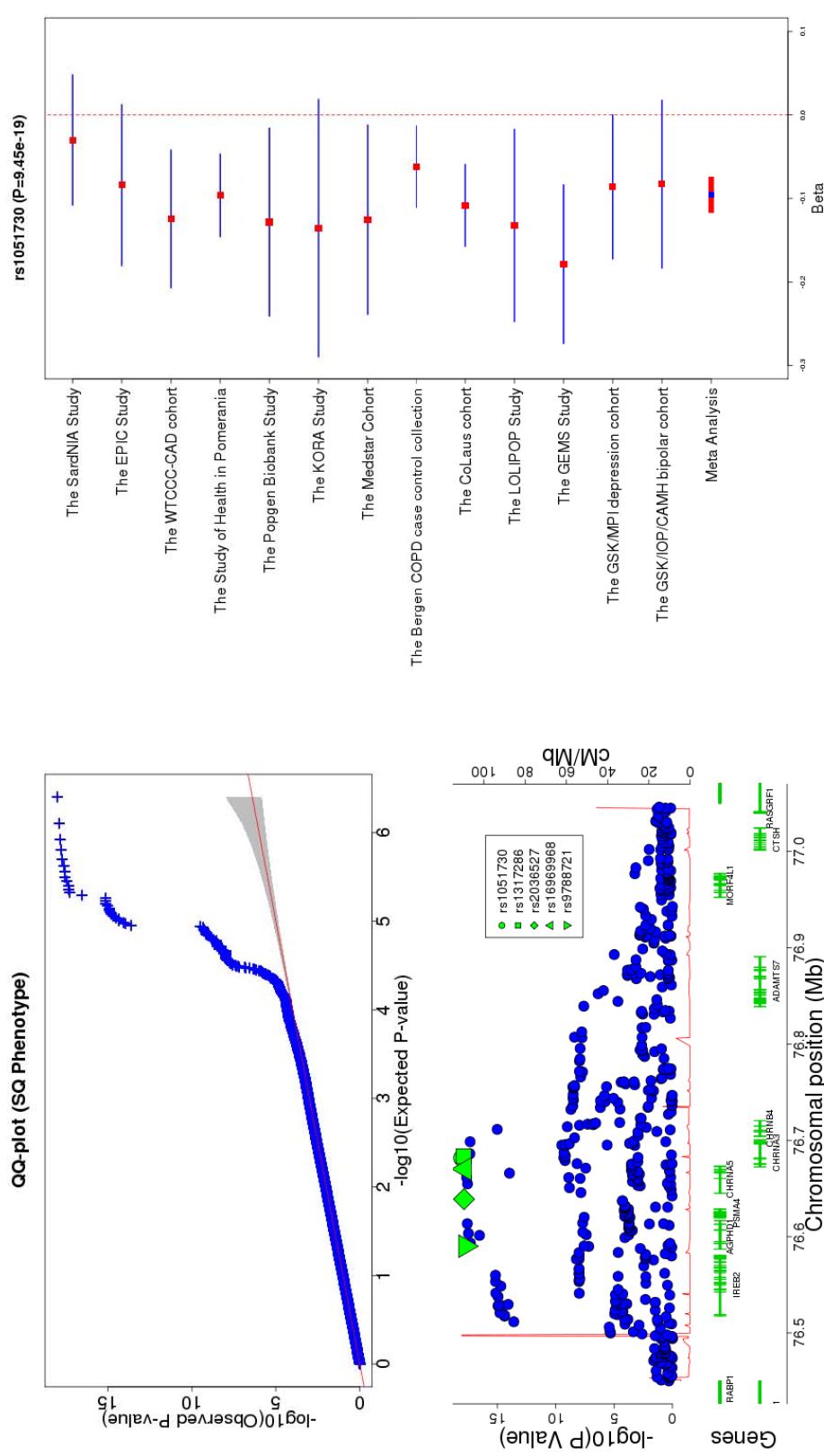
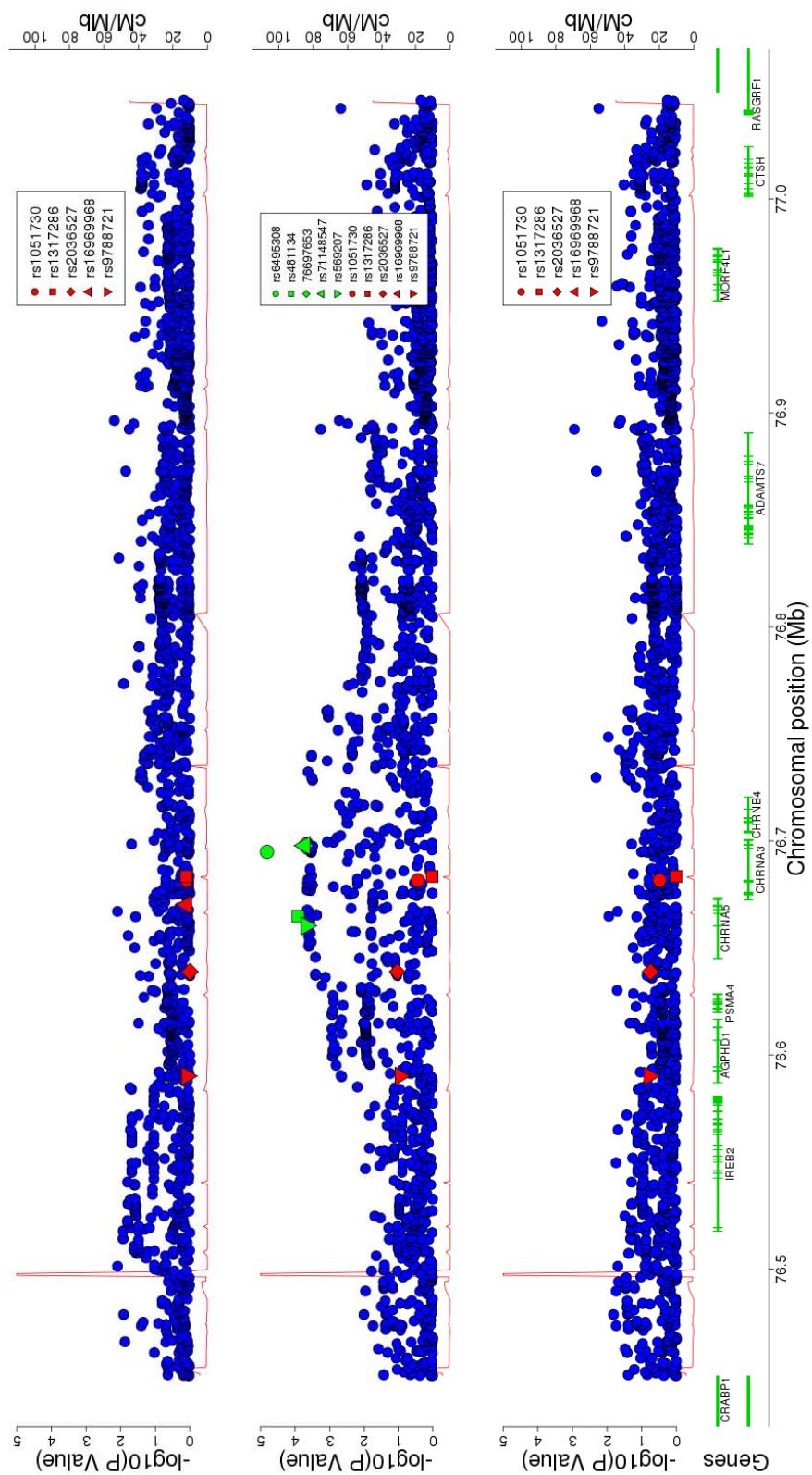


SUPPLEMENTARY ONLINE MATERIAL

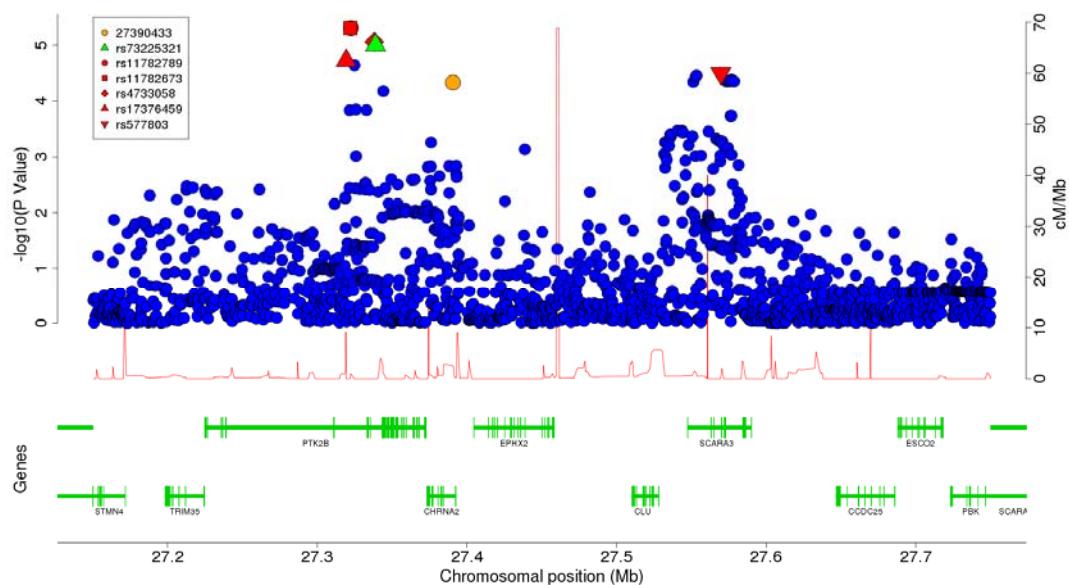
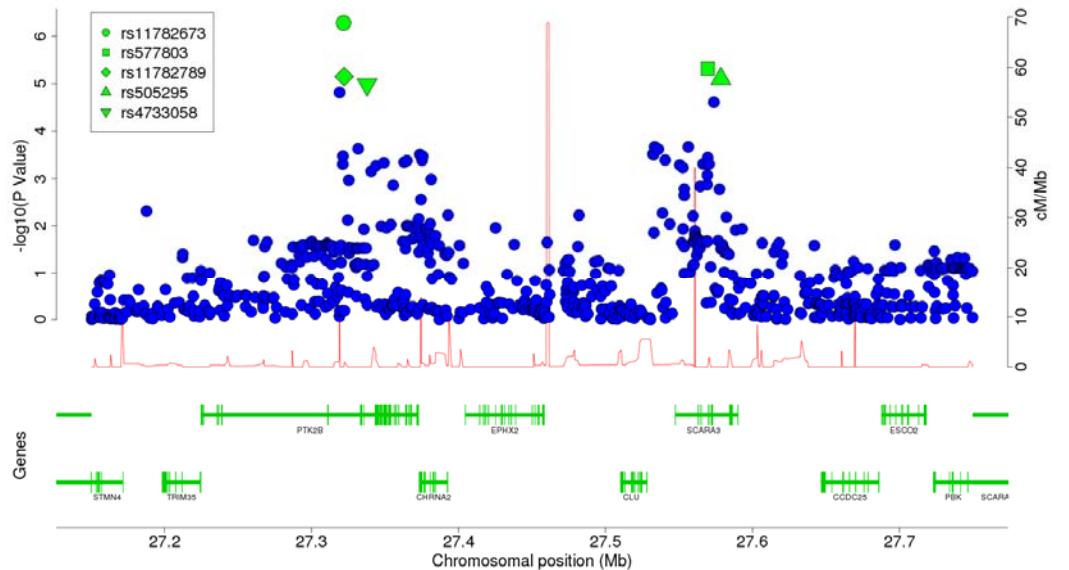
LIU *et al.*, Meta-analysis and imputation refines the association of 15q25 with smoking quantity



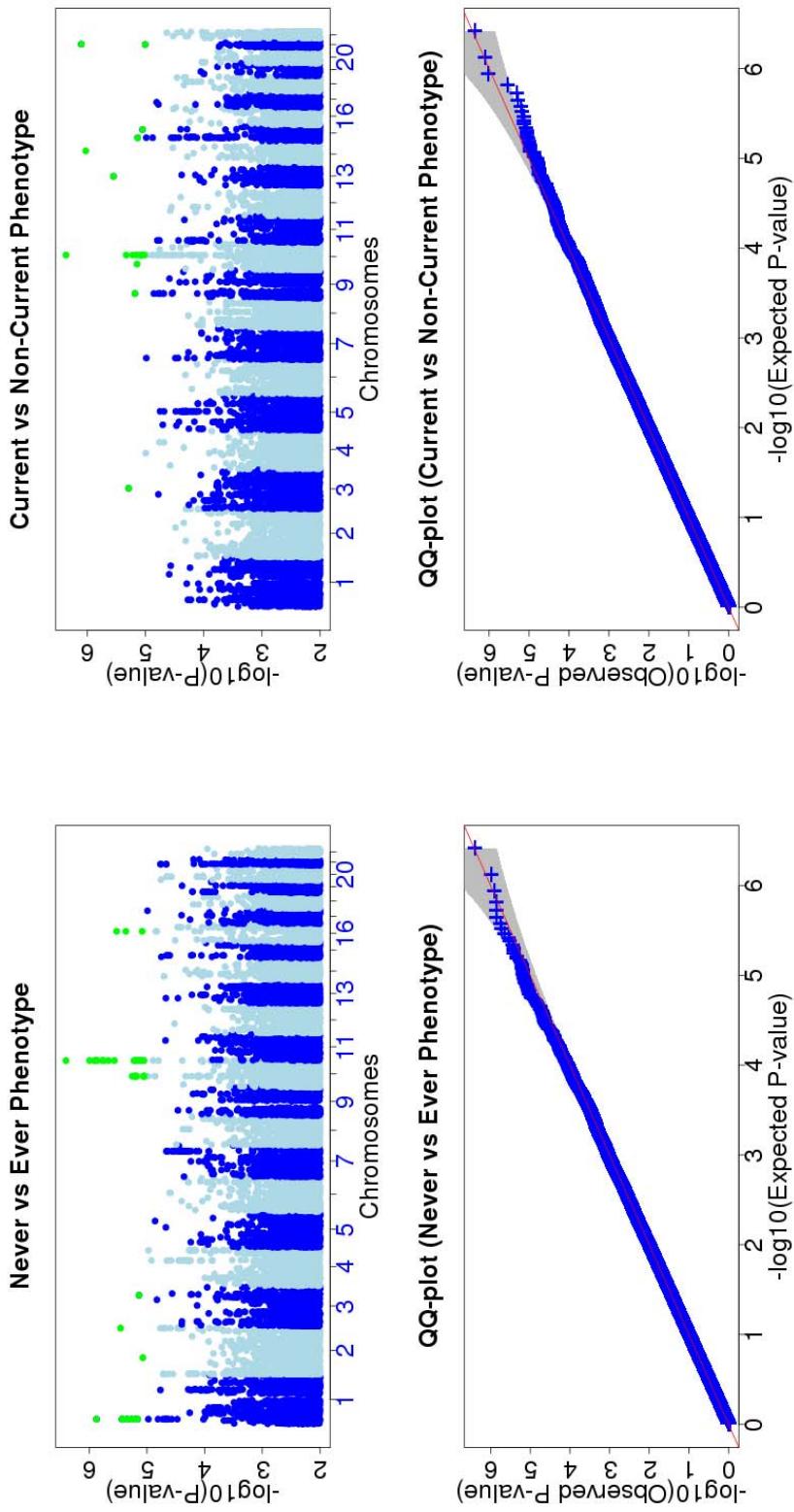
Supplementary Figure 1. Results from Smoking Quantity genome scan relating to 15q25. **Top left:** QQ plot showing significance of association of all SNPs in the genome-wide SQ meta-analysis versus that expected under the null hypothesis. **Bottom left:** Chromosome 15q25 signal plot based on HapMap imputation and association meta-analysis of SQ. SNPs are plotted on the x-axis by their positions on the chromosome, against association ($-\log_{10}$ p-value) with SQ on the left y-axis. The five SNPs with the lowest p-values are highlighted in green and their rs identities are given in the box. Recombination rates across the region are shown by the red line plotted against the right y-axis. Genes and the position of exons are shown at the bottom (using data from the UCSC genome browser, genome.ucsc.edu). **Right:** Forest plot showing by-cohort evidence of association with SQ at SNP rs1051730. Point estimates of beta for the G allele together with the 95% confidence interval (CI) are shown for each cohort. The meta-analysis estimate with its 95% CI is shown at the bottom of the plot.



Supplementary Figure 2. Conditional analysis of 15q25. **Top:** Chromosome 15q25 signal plot based on 1000 Genomes imputation and meta-analysis of SQ, conditional on SNPs rs55853698 and rs6495308. SNPs are plotted on the x-axis by their positions on the chromosome, against association with SQ on the left y-axis ($-\log_{10}$ p-value). The five SNPs with the lowest p-values from the unconditional HapMap-imputation analysis are highlighted in red. The rs identities of highlighted SNPs are given in the box. Recombination rates across the region are shown by the red line plotted against the right y-axis. Genes and the position of exons are shown at the bottom (using data from the UCSC genome browser). **Middle:** Chromosome 15q25 signal plot based on 1000 Genomes imputation and meta-analysis of SQ association, conditional on SNP rs16969968. The five SNPs with the lowest p-values from the conditional analysis are highlighted in green. The five SNPs with the lowest p-values from the unconditional HapMap-imputation analysis are highlighted in red. **Bottom:** Chromosome 15q25 signal plot based on 1000 Genomes imputation and meta-analysis of association with SQ, conditional on rs16969968 and rs588765. The five SNPs with the lowest p-values from the unconditional HapMap-imputation analysis are highlighted in red.



Supplementary Figure 3. Association signal on 8q21. **Top:** Chromosome 8q21 signal plot based on HapMap imputation and meta-analysis of association with SQ. SNPs are plotted on the x-axis by their positions on the chromosome, against association with SQ on the left y-axis ($-\log_{10} p\text{-value}$). The five SNPs with the lowest p-values are highlighted in green and their rs identities are given in the box. Recombination rates across the region are shown by the red line plotted against the right y-axis. Genes and the position of exons are shown below (using data from the UCSC genome browser, genome.ucsc.edu). **Bottom:** Chromosome 8q21 signal plot based on 1000 Genomes imputation and meta-analysis of SQ association. The five SNPs with the lowest p-values from the HapMap imputation are highlighted in red. The five SNPs with the lowest p-values from 1000 Genomes imputation are highlighted in green (unless already colored red). A novel CHRNA2 SNP at position 27390433 is highlighted in yellow.



Supplementary Figure 4. Analysis of EVER/Never and Current/Non-current. **Top left:** Manhattan plot showing significance of association of all SNPs in the EVER/NEVER genome-wide meta-analysis. SNPs are plotted on the x-axis according to their positions on each chromosome, against association with EVER/NEVER status on the y-axis ($-\log_{10}$ P-value). SNPs with p-values less than 1.0E-05 are highlighted in green. **Bottom left:** QQ plot showing significance of association of all SNPs in the EVER/NEVER genome-wide meta-analysis versus that expected under the null hypothesis. **Top right:** Manhattan plot showing significance of association of all SNPs in the Current/Non-Current genome-wide meta-analysis. **Bottom right:** QQ plot showing significance of association of all SNPs in the Current/Non-Current genome-wide meta-analysis versus that expected under the null hypothesis.

Supplementary Table 1. Information on study cohorts used in meta-analysis (Table covers 2 pages).

Imputation Software	Post-imputation #SNPs	Association Analysis Software	Covariates used in analysis	Total sample size		CPD phenotype (maximal, average, n/a)	Sample Size for CPD > 0	CPD Mean (SD) for CPD>0 samples	Sample Size		Sample Size		
				Male	Female				All	All	Ever	Never	
IMPUTE	2614446	SNPTEST	Sex, Age	470	1390	n/a	n/a	n/a	n/a	n/a	262	558	WTCCC-RA
IMPUTE	2549220	SNPTEST	Sex, Age, Case-control status	1608	1908	n/a	n/a	n/a	1927	1589	353	1574	EPIC
IMPUTE	2614446	SNPTEST	Sex, Age	775	1177	maximal	830	17.2(11.9)	n/a	n/a	1274	672	WTCCC-HT
IMPUTE	2600508	SNPTEST	Sex, Age, Case-control status, Country	1094	753	maximal	862	19.1(12.8)	910	793	268	642	GSK-GEMS
IMPUTE	2565431	SNPTEST	Sex, Age, Case-control status	901	732	average	1632	14.6(7.8)	n/a	n/a	725	905	GSK-COPD
IMPUTE	2547468	SNPTEST	Sex, Age, Case-control status	697	1108	maximal	944	15.5(11.7)	1008	790	498	510	GSK-BIPOLAR
IMPUTE	2549858	SNPTEST	Sex, Age, Case-control status	589	1203	maximal	899	17.9(11.9)	935	856	503	432	GSK-UNIPOLAR
IMPUTE	2614446	SNPTEST	Sex, Age	680	1068	n/a	n/a	n/a	713	540	713	420	WTCCC-IBD
IMPUTE	2597224	SNPTEST	Sex, Age	813	831	maximal	253	16.7(9.4)	811	831	217	1425	KORA
MACH	2543888	ProbABEL	covariates	300	527	n/a	n/a	n/a	376	451	179	654	KORCULA
IMPUTE	2711866	SNPTEST	Sex, Age, Race	969	319	maximal	650	17.1(13.5)	653	635	258	395	GSK-LOLIPOP
IMPUTE	2739753	SNPTEST	Sex, Age, Case-control status	857	465	maximal	820	25.1(16.6)	853	469	300	553	GSK-MEDSTAR
MACH	2543888	ProbABEL	covariates	322	370	n/a	n/a	n/a	288	404	60	632	ORCADES
IMPUTE	2745959	SNPTEST	Sex, Age, Case-control status	932	469	n/a	n/a	n/a	n/a	n/a	464	612	PENNCAHT
	2726564	SNPTEST		620	487	average	573	16.3(11.5)	495	608	n/a	n/a	POPGEN
IMPUTE	2606530	SNPTEST	Sex, Age	2659	2977	maximal	3132	18.2(12.8)	3357	2275	1485	1872	GSK-LAUSANNE
MACH	2252250	MERLIN	Sex, Age, Age ²	1886	2419	average	1731	16.2(11.6)	1743	2562	873	3432	SardinIA
IMPUTE	2823150	SNPTEST	Sex, Age	2009	2071	average	2011	15.9(9.163)	2631	1449	1240	2840	SHIP
MACH	2543888	ProbABEL	covariates	323	446	n/a	n/a	n/a	441	328	212	557	VIS
IMPUTE	2614446	SNPTEST	Sex, Age	1527	399	average	1237	21.3(13.6)	1457	461	239	1218	WTCCC-CAD
				20031	21119		15574		18598	15041	10123	19903	TOTAL

Curr/Non-curr	5	rs6836368	4	130970736	A	G	0.95	1.74E-05	0.10	1.51E-01	NA	1.11E-04	0.184(0.0476)
Curr/Non-curr		rs9986009	4	130972303	C	T	0.95	2.09E-05	0.06	1.46E-01	NA	2.13E-04	0.184(0.0498)
Curr/Non-curr		rs13361876	5	93849707	A	C	0.27	3.95E-05	0.64	7.46E-01	NA	4.77E-03	0.045(0.0161)
Curr/Non-curr		rs10075161	5	93892792	C	T	0.27	2.10E-05	0.68	7.95E-01	NA	4.40E-03	0.045(0.0157)
Curr/Non-curr		rs1376713	5	93938613	C	G	0.83	3.34E-05	0.13	5.56E-01	NA	2.29E-03	-0.066(0.0216)
Curr/Non-curr		rs2122985	5	93998652	C	G	0.26	4.36E-05	0.55	9.58E-01	NA	9.00E-03	0.041(0.0155)
Curr/Non-curr		rs2122984	5	93998673	C	T	0.26	4.37E-05	0.55	9.58E-01	NA	9.02E-03	0.041(0.0155)
Curr/Non-curr		rs1390642	5	93998790	A	C	0.74	4.29E-05	0.55	9.59E-01	NA	8.93E-03	-0.041(0.0155)
Curr/Non-curr	6	rs7446179	5	93998933	A	G	0.26	4.41E-05	0.55	9.60E-01	NA	9.04E-03	0.041(0.0155)
Curr/Non-curr		rs12656300	5	93999343	A	G	0.26	4.72E-05	0.55	9.60E-01	NA	9.32E-03	0.040(0.0155)
Curr/Non-curr		rs12659597	5	94017075	A	G	0.73	1.80E-05	0.42	9.64E-01	NA	6.33E-03	-0.042(0.0155)
Curr/Non-curr		rs12655665	5	94017825	C	T	0.26	4.85E-05	0.56	9.66E-01	NA	9.65E-03	0.040(0.0155)
Curr/Non-curr		rs1124668	5	94038997	G	T	0.74	4.54E-05	0.60	9.36E-01	NA	9.05E-03	-0.041(0.0155)
Curr/Non-curr		rs2270626	5	94049772	C	G	0.74	4.53E-05	0.60	9.45E-01	NA	9.36E-03	-0.040(0.0155)
Curr/Non-curr		rs7718956	5	94069364	A	C	0.27	4.50E-05	0.58	8.24E-01	NA	6.57E-03	0.041(0.0151)
Curr/Non-curr		rs12515845	5	94094796	G	T	0.73	6.07E-05	0.32	7.87E-01	NA	6.95E-03	-0.042(0.0157)
Curr/Non-curr		rs2042545	7	7841970	C	T	0.52	3.66E-05	0.51	2.82E-01	NA	7.09E-02	0.024(0.0131)
Curr/Non-curr	7	rs6957269	7	7844302	A	G	0.50	1.04E-05	0.50	2.89E-01	NA	4.97E-02	-0.026(0.0132)
Curr/Non-curr		rs6961771	7	7844626	C	T	0.51	3.28E-05	0.46	4.01E-01	NA	5.05E-02	0.025(0.0129)
Curr/Non-curr		rs17505017	9	23795555	C	T	0.81	1.40E-05	0.85	4.92E-01	NA	2.78E-02	0.037(0.0166)
Curr/Non-curr		rs17484841	9	23796012	C	G	0.80	6.63E-06	0.78	5.04E-01	NA	1.94E-02	0.039(0.0165)
Curr/Non-curr		rs16907788	9	23798910	A	G	0.80	1.56E-05	0.86	4.87E-01	NA	2.85E-02	0.036(0.0166)
Curr/Non-curr	8	rs3793594	9	23800167	A	C	0.81	1.78E-05	0.83	4.80E-01	NA	3.34E-02	0.035(0.0165)
Curr/Non-curr		rs3793599	9	23801669	A	G	0.26	2.03E-05	0.83	5.04E-01	NA	3.23E-02	-0.035(0.0165)
Curr/Non-curr		rs3793601	9	23801903	G	T	0.26	2.08E-05	0.83	5.51E-01	NA	2.93E-02	-0.036(0.0165)
Curr/Non-curr		rs3793603	9	23803100	A	G	0.27	1.77E-05	0.85	5.14E-01	NA	2.81E-02	-0.036(0.0165)
Curr/Non-curr		rs6475757	9	23805155	C	G	0.81	2.87E-05	0.90	5.26E-01	NA	3.49E-02	0.035(0.0165)
Curr/Non-curr		rs4746143	10	75147304	A	G	0.73	7.08E-06	0.65	4.28E-01	NA	2.49E-02	0.033(0.0148)
Curr/Non-curr		rs7923045	10	75157504	A	T	0.60	2.63E-05	0.52	6.16E-01	NA	2.48E-02	0.029(0.0131)
Curr/Non-curr		rs10733894	10	75168673	G	T	0.73	8.09E-06	0.64	3.97E-01	NA	3.15E-02	0.031(0.0146)
Curr/Non-curr		rs11000765	10	75182458	C	G	0.36	8.43E-06	0.65	3.80E-01	NA	3.20E-02	-0.031(0.0145)
Curr/Non-curr		rs10740418	10	75189328	C	T	0.36	8.43E-06	0.65	3.73E-01	NA	3.26E-02	-0.031(0.0145)
Curr/Non-curr		rs12413039	10	75194765	C	G	0.36	4.33E-07	0.68	3.22E-01	NA	1.60E-02	-0.036(0.0149)
Curr/Non-curr		rs10762563	10	75194808	A	C	0.46	4.09E-05	0.46	6.56E-01	NA	2.62E-02	-0.029(0.0130)
Curr/Non-curr		rs3849969	10	75196005	A	G	0.70	4.71E-06	0.73	3.70E-01	NA	2.95E-02	0.032(0.0146)
Curr/Non-curr		rs4746148	10	75204494	C	T	0.71	8.84E-06	0.66	3.76E-01	NA	3.26E-02	0.031(0.0145)
Curr/Non-curr		rs2271271	10	75228873	A	G	0.36	1.31E-05	0.63	4.56E-01	NA	2.94E-02	-0.031(0.0144)
Curr/Non-curr		rs4691	10	75231922	C	T	0.72	1.33E-05	0.64	3.43E-01	NA	4.19E-02	0.030(0.0147)
Curr/Non-curr		rs13013	10	75232167	A	C	0.46	4.34E-05	0.48	7.09E-01	NA	2.31E-02	-0.030(0.0130)
Curr/Non-curr		rs3812637	10	75238852	C	T	0.71	1.58E-05	0.64	4.28E-01	NA	3.32E-02	0.031(0.0145)
Curr/Non-curr	9	rs7098573	10	75250020	A	G	0.34	2.26E-05	0.57	3.89E-01	NA	1.50E-04	-0.067(0.0178)
Curr/Non-curr		rs11000787	10	75254389	C	T	0.36	1.69E-05	0.64	4.20E-01	NA	3.41E-02	-0.031(0.0145)
Curr/Non-curr		rs2688617	10	75316153	A	T	0.75	4.17E-05	0.23	2.36E-01	NA	9.43E-02	0.025(0.0151)
Curr/Non-curr		rs2675677	10	75318255	A	C	0.33	1.76E-05	0.16	3.36E-01	NA	5.18E-02	-0.029(0.0148)
Curr/Non-curr		rs2688615	10	75321505	C	G	0.73	6.09E-06	0.34	2.27E-01	NA	5.76E-02	0.029(0.0151)
Curr/Non-curr		rs2633306	10	75322453	A	C	0.72	1.70E-05	0.27	2.12E-01	NA	8.11E-02	0.026(0.0150)
Curr/Non-curr		rs2688612	10	75323211	G	T	0.74	2.25E-05	0.23	2.26E-01	NA	8.48E-02	0.026(0.0148)
Curr/Non-curr		rs2688611	10	75323378	G	T	0.75	3.39E-05	0.25	1.80E-01	NA	1.16E-01	0.024(0.0150)
Curr/Non-curr		rs2633309	10	75324092	A	G	0.33	9.62E-06	0.25	1.96E-01	NA	7.71E-02	-0.026(0.0148)
Curr/Non-curr		rs2688607	10	75333742	A	G	0.72	2.85E-05	0.12	1.19E-01	NA	1.61E-01	0.021(0.0149)
Curr/Non-curr		rs2633298	10	75336345	C	G	0.73	1.06E-05	0.26	1.61E-01	NA	9.86E-02	0.024(0.0148)
Curr/Non-curr		rs2459449	10	75339019	C	T	0.33	2.04E-05	0.29	1.43E-01	NA	1.31E-01	-0.023(0.0150)
Curr/Non-curr		rs2227551	10	75339196	G	T	0.74	3.17E-05	0.36	2.39E-01	NA	9.91E-02	0.025(0.0149)
Curr/Non-curr		rs12281511	11	12633871	A	C	0.48	1.61E-05	0.38	3.54E-01	NA	6.42E-04	-0.046(0.0134)
Curr/Non-curr		rs7926971	11	12654616	A	G	0.46	3.71E-05	0.42	4.64E-01	NA	1.71E-03	-0.040(0.0126)
Curr/Non-curr		rs10765987	11	12662319	C	T	0.44	1.76E-05	0.22	7.11E-01	NA	2.78E-03	-0.038(0.0128)
Curr/Non-curr		rs7168832	15	36987749	C	G	0.56	3.79E-05	0.78	5.95E-01	NA	2.93E-02	-0.028(0.0128)
Curr/Non-curr		rs12439991	15	36988358	A	G	0.45	3.27E-05	0.78	5.79E-01	NA	2.84E-02	0.028(0.0128)
Curr/Non-curr		rs724234	15	36992739	A	G	0.46	7.38E-06	0.85	3.41E-01	NA	4.03E-02	0.027(0.0129)
Curr/Non-curr	11	rs7162298	15	36993927	A	G	0.55	3.04E-05	0.85	4.40E-01	NA	4.41E-02	-0.026(0.0128)
Curr/Non-curr		rs7181150	15	37000183	C	T	0.46	2.77E-05	0.62	3.33E-01	NA	5.54E-02	0.025(0.0129)
Curr/Non-curr		rs11070160	15	37000434	A	G	0.53	1.34E-05	0.75	3.41E-01	NA	4.62E-02	-0.025(0.0127)
Curr/Non-curr		rs10851370	15	37000464	G	T	0.47	1.04E-05	0.74	3.29E-01	NA	4.61E-02	0.025(0.0128)
Curr/Non-curr	12	rs16948215	17	13491726	G	T	0.18	1.68E-05	0.74	3.66E-01	NA	7.66E-04	-0.096(0.0284)
Curr/Non-curr		rs12326022	17	24405383	G	T	0.93	1.57E-05	0.57	8.25E-01	NA	4.37E-03	-0.100(0.0351)
Curr/Non-curr		rs6005312	22	25878374	C	T	0.80	4.93E-05	0.41	9.83E-01	NA	1.17E-02	-0.042(0.0168)
Curr/Non-curr	14	rs9625159	22	25882564	C	T	0.80	2.99E-05	0.49	3.99E-01	NA	8.18E-04	-0.058(0.0173)
Curr/Non-curr		rs10427939	22	25883126	C	T	0.19	5.39E-05	0.14	1.44E-01	NA	1.57E-04	0.112(0.0297)
Curr/Non-curr		rs1474745	22	42680569	C	T	0.75	2.34E-05	0.94	9.08E-01	NA	6.61E-03	-0.046(0.0169)
Curr/Non-curr		rs3761472	22	42699455	A	G	0.22	3.52E-05	0.97	9.15E-01	NA	8.32E-03	0.044(0.0168)

Supplementary Table 3. Genomic control lambda inflation factors

Study Name	Other Name	GC lambda inflation factor		
		Ever vs Never	Current vs Non-current	CPD
The arc Epidemiology Unit Rheumatoid Arthritis cohort	WTCCC-RA	n/a	0.993213	n/a
The EPIC Obesity study	EPIC	1.012	0.9948708	n/a
The BRIGHT Study	WTCCC-HT	n/a	1.00569	1.000426
The GEMS Study	GEMS	1.013301	0.9955785	1.019739
The Bergen COPD case control collection	GSK-COPD	n/a	0.9855785	0.9960527
The GSK/IOP/CAMH bipolar cohort	GSK-BIPOLAR	0.9961354	0.9997034	1.003575
The GSK/MPI depression cohort	GSK-UNIPOLAR	1.010012	1.010608	1.012388
The UK IBD Genetics Consortium	WTCCC-IBD	1.004875	1.008234	n/a
The KORA Study	KORA	1.027964	0.9975758	1.030356
The KORCULA Study	KORCULA	1.072233	1.037129	n/a
The LOLIPOP Study	LOLIPOP	1.026318	1.008084	1.008873
The Medstar Cohort	MEDSTAR	0.9924291	0.9961729	1.009704
The Orkney Complex Disease Study	ORCADES	1.128765	1.079304	n/a
The PennCATH cohort	PENNCAHT	n/a	0.951226	n/a
The Popgen Biobank Study	POPGEN	1.018822	n/a	1.035871
The PsyCoLaus cohort	CoLaus	1.019417	1.012127	1.0131102
The SardinIA study	SardiNIA	1.135018	1.097244	1.088316
The Study of Health in Pomerania	SHIP	1.000568	1.022989	1.006505
The VIS Study	VIS	1.055634	1.03443	n/a
The WTCCC-CAD cohort	WTCCC-CAD	1.009498	0.9964745	1.010912
COMBINED		1.002404	0.9982071	1.014531

SUPPLEMENTARY NOTE

Comparison of SQ and CPD phenotype

We also carried out the meta-analysis of our cohort using CPD as the phenotype as this was used by the ENGAGE study. The manhattan plot for the genome-wide screen is shown in Figure S13. This clearly highlights the chromosome 15 region but the p-values are not as significant as those obtained when using SQ as the phenotype (rs1051730 has a p-value of 4.65E-16 for the CPD phenotype but 9.45E-19 for the SQ phenotype). Figure S14 shows the chromosome 15 region in more detail and shows that the top 5 SNPs are the same for both phenotypes but that there is a slight change in the order of the SNPs. This effect can be explained by the discrete nature of the SQ phenotype i.e the SQ level 3 is defined as all values of CPD of 31 or more so that the upper tail of the CPD distribution is effectively truncated. When using CPD as the phenotype individuals with high values of CPD, such as outlying observations, may elevate the residual variance of the phenotype which will tend to reduce the significance of associations. The use of the SQ phenotype will be more robust to this effect.

Acknowledgements for individual cohorts

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Membership of the Wellcome Trust Case Control Consortium (60. In the author list annotation):

Management Committee: Paul R Burton¹, David G Clayton², Lon R Cardon³, Nick Craddock⁴, Panos Deloukas⁵, Audrey Duncanson⁶, Dominic P Kwiatkowski^{3,5}, Mark I McCarthy^{3,7}, Willem H Ouwehand^{8,9}, Nilesh J Samani¹⁰, John A Todd², Peter Donnelly (Chair)¹¹

Data and Analysis Committee: Jeffrey C Barrett³, Paul R Burton¹, Dan Davison¹¹, Peter Donnelly¹¹, Doug Easton¹², David M. Evans³, Hin-Tak Leung², Jonathan L Marchini¹¹, Andrew P Morris³, Chris CA Spencer¹¹, Martin D Tobin¹, Lon R Cardon (Co-chair)³, David G Clayton (Co-chair)²

UK Blood Services & University of Cambridge Controls: Antony P Attwood^{5,8}, James P Boorman^{8,9}, Barbara Cant⁸, Ursula Everson¹³, Judith M Hussey¹⁴, Jennifer D Jolley⁸, Alexandra S Knight⁸, Kerstin Koch⁸, Elizabeth Meech¹⁵, Sarah Nutland², Christopher V Prowse¹⁶, Helen E Stevens², Niall C Taylor⁸, Graham R Walters¹⁷, Neil M Walker², Nicholas A Watkins^{8,9}, Thilo Winzer⁸, John A Todd², Willem H Ouwehand^{8,9}

1958 Birth Cohort Controls: Richard W Jones¹⁸, Wendy L McArdle¹⁸, Susan M Ring¹⁸, David P Strachan¹⁹, Marcus Pembrey^{18,20}

Bipolar Disorder (Aberdeen): Gerome Breen²¹, David St Clair²¹; **(Birmingham):** Sian Caesar²², Katherine Gordon-Smith^{22,23}, Lisa Jones²²; **(Cardiff):** Christine Fraser²³, Elaine K Green²³, Detelina Grozeva²³, Marian L Hamshire²³, Peter A Holmans²³, Ian R Jones²³, George Kirov²³, Valentina Moskvina²³, Ivan Nikolov²³, Michael C O'Donovan²³, Michael J Owen²³, Nick Craddock²³; **(London):** David A Collier²⁴, Amanda Elkin²⁴, Anne Farmer²⁴, Richard Williamson²⁴, Peter McGuffin²⁴; **(Newcastle):** Allan H Young²⁵, I Nicol Ferrier²⁵

Coronary Artery Disease (Leeds): Stephen G Ball²⁶, Anthony J Balmforth²⁶, Jennifer H Barrett²⁶, D Timothy Bishop²⁶, Mark M Iles²⁶, Azhar Maqbool²⁶, Nadira Yuldasheva²⁶, Alistair S Hall²⁶; **(Leicester):** Peter S Braund¹⁰, Paul R Burton¹, Richard J Dixon¹⁰, Massimo Mangino¹⁰, Suzanne Stevens¹⁰, Martin D Tobin¹, John R Thompson¹, Nilesh J Samani¹⁰

Crohn's Disease (Cambridge): Francesca Bredin²⁷, Mark Tremelling²⁷, Miles Parkes²⁷; **(Edinburgh):** Hazel Drummond²⁸, Charles W Lees²⁸, Elaine R Nimmo²⁸, Jack Satsangi²⁸; **(London):** Sheila A Fisher²⁹, Alastair Forbes³⁰, Cathryn M Lewis²⁹, Clive M Onnie²⁹, Natalie J Prescott²⁹, Jeremy Sanderson³¹, Christopher G Mathew²⁹; **(Newcastle):** Jamie Barbour³², M Khalid Mohiuddin³², Catherine E Todhunter³², John C Mansfield³²; **(Oxford):** Tariq Ahmad³³, Fraser R Cummings³³, Derek P Jewell³³

Hypertension (Aberdeen): John Webster³⁴; **(Cambridge):** Morris J Brown³⁵, David G Clayton²; **(Evry, France):** G Mark Lathrop³⁶; **(Glasgow):** John Connell³⁷, Anna Dominiczak³⁷; **(Leicester):** Nilesh J Samani¹⁰; **(London):** Carolina A Braga Marciano³⁸, Beverley Burke³⁸, Richard Dobson³⁸, Johannie Gungadoo³⁸, Kate L Lee³⁸, Patricia B Munroe³⁸, Stephen J Newhouse³⁸, Abiodun Onipinla³⁸, Chris Wallace³⁸, Mingzhan Xue³⁸, Mark Caulfield³⁸; **(Oxford):** Martin Farrall³⁹

Rheumatoid Arthritis: Anne Barton⁴⁰, Ian N Bruce⁴⁰, Hannah Donovan⁴⁰, Steve Eyre⁴⁰, Paul D Gilbert⁴⁰, Samantha L Hider⁴⁰, Anne M Hinks⁴⁰, Sally L John⁴⁰, Catherine Potter⁴⁰, Alan J Silman⁴⁰, Deborah PM Symmons⁴⁰, Wendy Thomson⁴⁰, Jane Worthington⁴⁰

Type 1 Diabetes: David G Clayton², David B Dunger^{2 41}, Sarah Nutland², Helen E Stevens², Neil M Walker², Barry Widmer^{2 41}, John A Todd²

Type 2 Diabetes (Exeter): Timothy M Frayling^{42 43}, Rachel M Freathy^{42 43}, Hana Lango^{42 43}, John R B Perry^{42 43}, Beverley M Shields⁴³, Michael N Weedon^{42 43}, Andrew T Hattersley^{42 43}; (**London:**) Graham A Hitman⁴⁴; (**Newcastle:**) Mark Walker⁴⁵; (**Oxford:**) Kate S Elliott^{3 7}, Christopher J Groves⁷, Cecilia M Lindgren^{3 7}, Nigel W Rayner^{3 7}, Nicholas J Timpson^{3 46}, Eleftheria Zeggini^{3 7}, Mark I McCarthy^{3 7},

Tuberculosis (Gambia): Melanie Newport⁴⁷, Giorgio Sirugo⁴⁷; (**Oxford:**) Emily Lyons³, Fredrik Vannberg³, Adrian VS Hill³

Ankylosing Spondylitis: Linda A Bradbury⁴⁸, Claire Farrar⁴⁹, Jennifer J Pointon⁴⁸, Paul Wordsworth⁴⁹, Matthew A Brown^{48 49},

AutoImmune Thyroid Disease: Jayne A Franklyn⁵⁰, Joanne M Heward⁵⁰, Matthew J Simmonds⁵⁰, Stephen CL Gough⁵⁰

Breast Cancer: Sheila Seal⁵¹, Michael R Stratton^{51 52}, Nazneen Rahman⁵¹

Multiple Sclerosis: Maria Ban⁵³, An Goris⁵³, Stephen J Sawcer⁵³, Alastair Compston⁵³

Gambian Controls (Gambia): David Conway⁴⁷, Muminatou Jallow⁴⁷, Melanie Newport⁴⁷, Giorgio Sirugo⁴⁷; (**Oxford:**) Kirk A Rockett³, Dominic P Kwiatkowski^{3 5},

DNA, Genotyping, Data QC and Informatics (Wellcome Trust Sanger Institute, Hinxton): Suzannah J Bumpstead⁵, Amy Chaney⁵, Kate Downes^{2 5}, Mohammed JR Ghori⁵, Rhian Gwilliam⁵, Sarah E Hunt⁵, Michael Inouye⁵, Andrew Keniry⁵, Emma King⁵, Ralph McGinnis⁵, Simon Potter⁵, Rathi Ravindrarajah⁵, Pamela Whittaker⁵, Claire Widden⁵, David Withers⁵, Panos Deloukas⁵; (**Cambridge:**) Hin-Tak Leung², Sarah Nutland², Helen E Stevens², Neil M Walker², John A Todd² **Statistics (Cambridge):** Doug Easton¹², David G Clayton²; (**Leicester:**) Paul R Burton¹, Martin D Tobin¹; (**Oxford:**) Jeffrey C Barrett³, David M Evans³, Andrew P Morris³, Lon R Cardon³; (**Oxford:**) Niall J Cardin¹¹, Dan Davison¹¹, Teresa Ferreira¹¹, Joanne Pereira-Gale¹¹, Ingeleif B Hallgrimsdóttir¹¹, Bryan N Howie¹¹, Jonathan L Marchini¹¹, Chris CA Spencer¹¹, Zhan Su¹¹, Yik Ying Teo^{5 11}, Damjan Vukcevic¹¹, Peter Donnelly¹¹ **PIs:** David Bentley^{5 54}, Matthew A Brown^{48 49}, Lon R Cardon³, Mark Caulfield³⁸, David G Clayton², Alistair Compston⁵³, Nick Craddock²³, Panos Deloukas⁵, Peter Donnelly¹¹, Martin Farrall³⁹, Stephen CL Gough⁵⁰, Alistair S Hall²⁶, Andrew T Hattersley^{42 43}, Adrian VS Hill³, Dominic P Kwiatkowski^{3 5}, Christopher G Mathew²⁹, Mark I McCarthy^{3 7}, Willem H Ouwehand^{8 9}, Miles Parkes²⁷, Marcus Pembrey^{18 20}, Nazneen Rahman⁵¹, Nilesh J Samani¹⁰, Michael R Stratton^{51 52}, John A Todd², Jane Worthington⁴⁰

Affiliations: 1 *Genetic Epidemiology Group, Department of Health Sciences, University of Leicester, Adrian Building, University Road, Leicester, LE1 7RH, UK*; 2 *Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Wellcome Trust/MRC Building, Cambridge, CB2 0XY, UK*; 3 *Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK*; 4 *Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK*; 5 *The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK*; 6 *The Wellcome Trust, Gibbs Building, 215 Euston Road, London NW1 2BE, UK*; 7 *Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford, OX3 7LJ, UK*; 8 *Department of Haematology, University of Cambridge, Long Road, Cambridge, CB2 2PT, UK*; 9 *National Health Service Blood and Transplant, Cambridge Centre, Long*

Road, Cambridge, CB2 2PT, UK; 10 Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK; 11 Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK; 12 Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK; 13 National Health Service Blood and Transplant, Sheffield Centre, Longley Lane, Sheffield S5 7JN, UK; 14 National Health Service Blood and Transplant, Brentwood Centre, Crescent Drive, Brentwood, CM15 8DP, UK; 15 The Welsh Blood Service, Ely Valley Road, Talbot Green, Pontyclun, CF72 9WB, UK; 16 The Scottish National Blood Transfusion Service, Ellen's Glen Road, Edinburgh, EH17 7QT, UK; 17 National Health Service Blood and Transplant, Southampton Centre, Coxford Road, Southampton, SO16 5AF, UK; 18 Avon Longitudinal Study of Parents and Children, University of Bristol, 24 Tyndall Avenue, Bristol, BS8 1TQ, UK; 19 Division of Community Health Services, St George's University of London, Cranmer Terrace, London SW17 0RE, UK; 20 Institute of Child Health, University College London, 30 Guilford St, London WC1N 1EH, UK; 21 University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK; 22 Department of Psychiatry, Division of Neuroscience, Birmingham University, Birmingham, B15 2QZ, UK; 23 Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK; 24 SGDP, The Institute of Psychiatry, King's College London, De Crespigny Park Denmark Hill London SE5 8AF, UK; 25 School of Neurology, Neurobiology and Psychiatry, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK; 26 LIGHT and LIMM Research Institutes, Faculty of Medicine and Health, University of Leeds, Leeds, LS1 3EX, UK; 27 IBD Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 2QQ, UK; 28 Gastrointestinal Unit, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU UK; 29 Department of Medical & Molecular Genetics, King's College London School of Medicine, 8th Floor Guy's Tower, Guy's Hospital, London, SE1 9RT, UK; 30 Institute for Digestive Diseases, University College London Hospitals Trust, London, NW1 2BU, UK; 31 Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, SE1 7EH, UK; 32 Department of Gastroenterology & Hepatology, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK; 33 Gastroenterology Unit, Radcliffe Infirmary, University of Oxford, Oxford, OX2 6HE, UK; 34 Medicine and Therapeutics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Grampian AB9 2ZB, UK; 35 Clinical Pharmacology Unit and the Diabetes and Inflammation Laboratory, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK; 36 Centre National de Genotypage, 2, Rue Gaston Cremieux, Evry, Paris 91057.; 37 BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK; 38 Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine, Charterhouse Square, London EC1M 6BQ, UK; 39 Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK; 40arc Epidemiology Research Unit, University of Manchester, Stopford Building, Oxford Rd, Manchester, M13 9PT, UK; 41 Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK; 42 Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical School, Magdalen Road, Exeter EX1 2LU UK; 43 Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, Barrack Road, Exeter EX2 5DU UK; 44 Centre for Diabetes and Metabolic Medicine, Barts and The London, Royal London Hospital, Whitechapel, London, E1 1BB UK; 45 Diabetes Research Group, School of Clinical Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK; 46 The MRC Centre for Causal Analyses in Translational Epidemiology, Bristol University, Canyngate Hall, Whiteladies Rd, Bristol BS2 8PR, UK; 47 MRC Laboratories, Fajara, The Gambia; 48 Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Woolloongabba, Qld 4102, Australia; 49 Botnar Research Centre, University of Oxford, Headington, Oxford OX3 7BN, UK; 50 Department of Medicine, Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK; 51 Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Road, Sutton, SM2 5NG, UK; 52 Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; 53 Department of Clinical

*Neurosciences, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK; 54
PRESENT ADDRESS: Illumina Cambridge, Chesterford Research Park, Little Chesterford, Nr Saffron
Walden, Essex, CB10 1XL, UK*