Supplementary Information

Meta-analysis of three genome-wide association studies identifies susceptibility loci for colorectal cancer at 1q41, 3q26.2, 12q13.13 and 20q13.33

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Supplementary Table 1: Summary of the sample sets used in the study.

Note that small differences may exist between the numbers of patients available and the number of samples eventually analysed, owing to stringent QC measures. (References for this Table are provided in: Tomlinson, I et al. COGENT (COlorectal cancer GENeTics): an international consortium to study the role of polymorphic variation on the risk of colorectal cancer. Br J Cancer. 2010; 102: 447-454.)

Location	Study name	Sample sets used in this study	Sampling	No. Cases	No. Controls
Oxford University	VICTOR, post-treatment stage of a Phase III, randomised controlled trial of rofecoxib (VIOXX) in colorectal cancer patients after potentially curative therapy. QUASAR2, multicentre study of capecitbine +/− bevacizumab as adjuvant CRC treatment. http://www.octo-oxford.org.uk/alltrials/	VQ	Clinic-based series	1432	0
Institute of Education	58BC (UK 1958 Birth Cohort) http://www.b58cgene.sgul.ac.uk/	58BC	Population-based series	0	2697
Institute of Cancer Research	NSCCG (National Study of Colorectal Cancer). http://www.icr.ac.uk/research/research_sections/cancer_genetics/cancer_genetics_teams/molecular_and_population_genetics/nsccg/index.shtml	UK2 UK3	Population-based UK study. Spouse controls from NSCCG and GELCAPS (Genetic Lung Cancer Predisposition Study)	2854 3025	2822 2985
Edinburgh University	COGS (Colorectal Cancer Genetics Susceptibility Study)	Scotland1	Population-based incident case series aged <55 at diagnosis. Population-based controls.	980	1002
Edinburgh University	SOCCS (Scottish Colorectal Cancer Study)	Scotland2 Scotland3	Population-based incident case series; Scotland. Cancer-free population controls.	2024 940	2092 975
Oxford University	CORGI (Colorectal Tumour Gene Identification Consortium)	UK1 UK4	Cases, most with with family history of CRC, ascertained through clinical genetics centres in the UK. Spouse controls with no personal or family history of CRC	922 621	929 1121
University of Cardiff	COIN, COIN-B http://public.ukcrn.org.uk/search/	COIN/NBS	Multicentre study of cetuximab and other therapies in metastatic CRC	2151	0
Cambridge University	NBS (UK National Blood Service Blood Donor samples) http://www.wtccc.org.uk/ccc1/participants.shtml	COIN/NBS	Unselected UK blood donors	0	2501
Cambridge University	UKSEARCH (Studies of Epidemiology and Risk Factors in Cancer Heredity) http://www.srl.cam.ac.uk/search/Homepage.htm	Cambridge	Population-based case–control study	2248	2209
University of Helsinki, Finland	FCCPS (Finnish Colorectal Cancer Predisposition Study) http://research.med.helsinki.fi/gsb/aaltonen/	Helsinki	Population-based study, south-eastern Finland	988	864

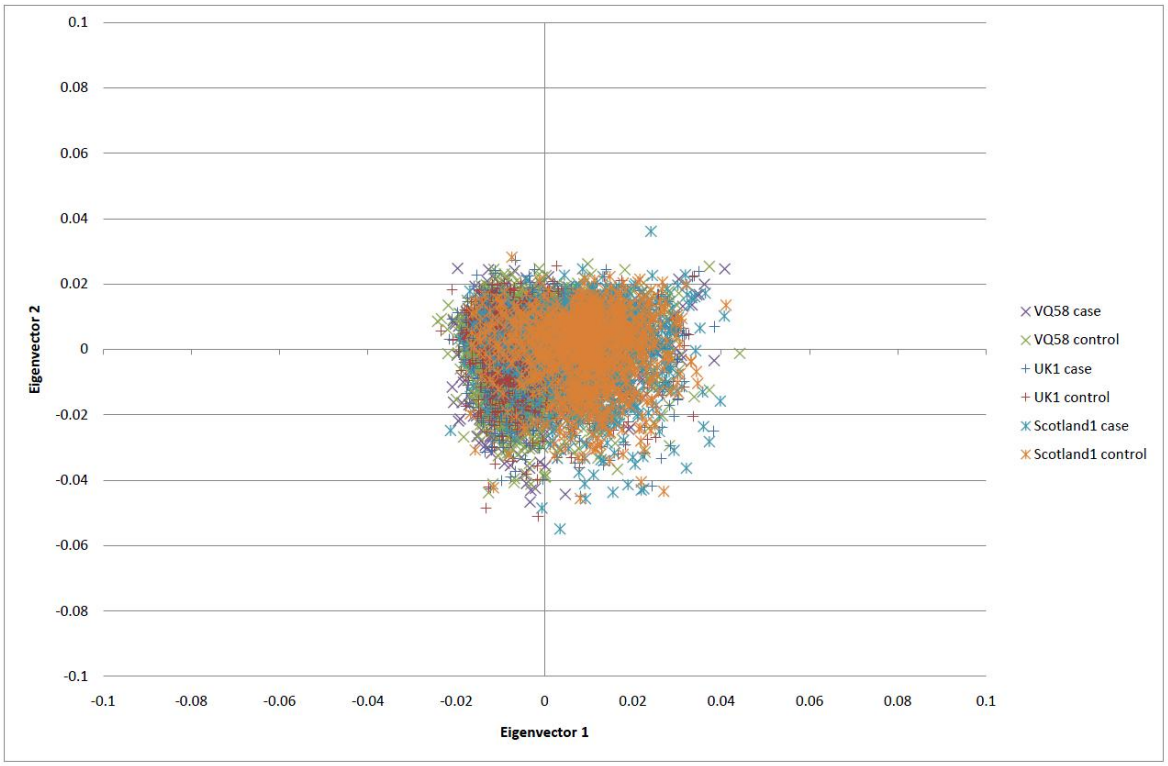
Supplementary Table 2: Results for seven SNPs selected for replication.

Allele frequencies and genotype counts are shown for each of the 11 sample series, together with summary statistics of association for each SNP under the allelic test. Note that rs11805285 was not genotyped in Scotland3 or Cambridge owing to results in UK that showed an OR of similar magnitude and in the opposite direction to that in the other sample sets; even had the Scotland3 and Cambridge series shown ORs similar to those in the 8 data sets providing support for this SNP, formal statistical significance would not have been achieved. This SNP may require validation in an even larger sample set. Ca=cases, Co=controls. 1=minor allele, 2=major allele. MAF=minor allele frequency. *P*=allelic P value from meta-analysis. OR=odds ratio. 11=minor allele homozygote, 12=heterozygote, 22=major allele homozygote. Phet=P value under test of sample series heterogeneity in the meta-analysis.

Summary	Series	Name	MAFca	MAFco	OR	Ca11	Ca12	Ca22	Co11	Co12	Co22
rs11805285	1	VQ58	0.12	0.14	0.823	18	305	1109	54	652	1988
chr1: 218,418,346	2	UK1/CORGI	0.13	0.15	0.874	18	202	700	21	228	680
z=3.95	3	Scotland1/COGS	0.13	0.16	0.780	10	225	741	26	259	716
$P=7.80x10^{-5}$	4	UK2/NSCCG	0.13	0.14	0.890	50	615	2187	49	684	2085
OR=0.92	5	Scotland2/SOCCS	0.13	0.14	0.939	32	470	1504	51	476	1530
95%CI=0.88-0.96	6	COIN/NBS	0.11	0.13	0.866	23	447	1680	47	557	1897
Phet=0.056	7	UK3/NSCCG	0.12	0.11	1.085	45	637	2293	19	598	2180
Allele 1=T	8	UK4/CORGI2BCD	0.13	0.14	0.924	6	118	364	20	259	769
Allele 2=C	9	Scotland3/SOCCS				Not genotyped owing to failure-to-replicate in UK3					
	10	Helsinki	0.08	0.09	0.900	9	134	791	3	141	676
	11	Cambridge				Not genotyped owing to failure-to-replicate in UK3					
rs6691170	1	VQ58	0.38	0.36	1.084	214	664	552	359	1239	1098
chr1: 220,112,069	2	UK1/CORGI	0.38	0.34	1.172	130	435	355	100	429	393
z=6.14	3	Scotland1/COGS	0.37	0.35	1.126	134	463	379	130	433	435
$P=9.55x10^{-10}$	4	UK2/NSCCG	0.38	0.36	1.122	398	1395	1058	355	1304	1159
OR=1.06	5	Scotland2/SOCCS	0.36	0.35	1.031	248	941	817	239	967	851
95%CI=1.04-1.08	6	COIN/NBS	0.38	0.36	1.090	300	1054	797	326	1170	1005
Phet=0.65	7	UK3/NSCCG	0.38	0.35	1.118	406	1442	1131	367	1244	1195
Allele 1=T	8	UK4/CORGI2BCD	0.36	0.35	1.034	71	212	213	130	474	447
Allele 2=G	9	Scotland3/SOCCS	0.36	0.37	0.975	103	376	326	117	447	363
	10	Helsinki	0.39	0.36	1.146	143	435	351	105	372	340
	11	Cambridge	0.39	0.36	1.138	324	1068	805	280	1013	890
rs6687758	1	VQ58	0.22	0.20	1.125	69	480	880	113	835	1746
chr1: 220,231,571	2	UK1/CORGI	0.21	0.20	1.098	37	312	568	32	299	598
z=5.97	3	Scotland1/COGS	0.22	0.20	1.169	63	308	606	34	325	642
$P=2.27x10^{-9}$	4	UK2/NSCCG	0.22	0.19	1.138	121	985	1746	98	898	1822
OR=1.09	5	Scotland2/SOCCS	0.21	0.19	1.133	77	694	1235	74	639	1344
95%CI=1.06-1.12	6	COIN/NBS	0.21	0.19	1.151	102	701	1330	89	770	1642
Phet=0.73	7	UK3/NSCCG	0.20	0.19	1.053	122	947	1920	115	850	1861
Allele 1=G	8	UK4/CORGI2BCD	0.21	0.20	1.104	24	158	306	45	309	669
Allele 2=A	9	Scotland3/SOCCS	0.22	0.22	0.958	48	263	519	51	315	566
	10	Helsinki	0.28	0.26	1.114	67	385	476	49	317	437
	11	Cambridge	0.21	0.19	1.165	89	755	1366	76	664	1444
rs10936599	1	VQ58	0.23	0.25	0.906	80	491	861	172	978	1547
chr3: 170,974,795	2	UK1/CORGI	0.20	0.24	0.785	42	288	591	49	355	525
z=5.52	3	Scotland1/COGS	0.23	0.26	0.815	57	324	588	66	396	539
$P=3.39x10^{-8}$	4	UK2/NSCCG	0.23	0.25	0.903	140	1027	1685	181	1033	1603
OR=0.93	5	Scotland2/SOCCS	0.24	0.25	0.930	112	739	1155	130	783	1144
95%CI=0.91-0.96	6	COIN/NBS	0.24	0.25	0.938	115	786	1250	152	936	1413
Phet=0.38	7	UK3/NSCCG	0.24	0.24	0.986	167	1075	1745	148	1057	1633
Allele 1=T	8	UK4/CORGI2BCD	0.22	0.25	0.849	28	208	354	62	403	575
Allele 2=C	9	Scotland3/SOCCS	0.22	0.24	0.897	42	267	482	51	348	534
	10	Helsinki	0.26	0.28	0.869	70	316	504	60	332	404
	11	Cambridge	0.23	0.25	0.914	113	804	1296	130	829	1227
rs7136702	1	VQ58	0.38	0.35	1.131	194	695	543	296	1292	1106
chr12: 49,166,483	2	UK1/CORGI	0.38	0.35	1.110	131	433	357	113	430	386
z=5.49	3	Scotland1/COGS	0.38	0.35	1.131	146	443	388	126	444	431
$P=4.02x10^{-8}$	4	UK2/NSCCG	0.37	0.35	1.083	380	1331	1140	329	1306	1183
OR=1.06	5	Scotland2/SOCCS	0.38	0.36	1.088	276	975	755	275	935	847
95%CI=1.04-1.08	6	COIN/NBS	0.36	0.35	1.044	287	893	844	321	1121	1059
Phet=0.98	7	UK3/NSCCG	0.37	0.35	1.059	402	1388	1190	359	1283	1180
Allele 1=T	8	UK4/CORGI2BCD	0.39	0.36	1.117	81	215	190	151	466	444
Allele 2=C	9	Scotland3/SOCCS	0.39	0.37	1.108	118	310	270	122	401	356
	10	Helsinki	0.32	0.29	1.147	103	389	436	72	334	414
	11	Cambridge	0.37	0.35	1.079	332	955	903	261	1015	906
rs11169552	1	VQ58	0.23	0.27	0.825	75	518	839	202	1049	1445
chr12: 49,441,930	2	UK1/CORGI	0.24	0.26	0.891	56	328	537	67	350	512
z=6.37	3	Scotland1/COGS	0.25	0.28	0.869	60	369	544	76	406	519
$P=1.89x10^{-10}$	4	UK2/NSCCG	0.26	0.27	0.947	209	1062	1580	199	1124	1494
OR=0.92	5	Scotland2/SOCCS	0.26	0.27	0.918	111	808	1087	152	821	1084
95%CI=0.90-0.95	6	COIN/NBS	0.26	0.27	0.969	135	818	1107	189	973	1338
Phet=0.16	7	UK3/NSCCG	0.25	0.28	0.885	167	1179	1625	214	1142	1463
Allele 1=T	8	UK4/CORGI2BCD	0.25	0.27	0.903	34	175	277	80	395	554
Allele 2=C	9	Scotland3/SOCCS	0.24	0.27	0.875	14	127	176	80	321	490
	10	Helsinki	0.34	0.41	0.737	103	407	401	153	356	303
	11	Cambridge	0.26	0.27	0.930	155	824	1241	163	853	1172
rs4925386	1	VQ58	0.31	0.32	0.921	141	595	696	284	1178	1232
chr20: 60,354,439	2	UK1/CORGI	0.27	0.32	0.809	58	386	477	89	410	430
z=6.37	3	Scotland1/COGS	0.28	0.32	0.848	71	403	489	98	440	463
$P=1.89x10^{-10}$	4	UK2/NSCCG	0.30	0.31	0.937	238	1217	1397	272	1206	1340
OR=0.93	5	Scotland2/SOCCS	0.29	0.31	0.898	172	827	1007	196	902	959
95%CI=0.91-0.95	6	COIN/NBS	0.31	0.31	1.001	191	933	1013	218	1101	1181
Phet=0.16	7	UK3/NSCCG	0.29	0.33	0.839	245	1226	1497	291	1256	1269
Allele 1=T	8	UK4/CORGI2BCD	0.30	0.31	0.920	47	255	285	103	454	491
Allele 2=C	9	Scotland3/SOCCS	0.29	0.32	0.873	70	339	404	101	407	433
	10	Helsinki	0.30	0.30	0.975	83	395	467	83	335	411
	11	Cambridge	0.29	0.31	0.885	166	952	1105	210	963	1026

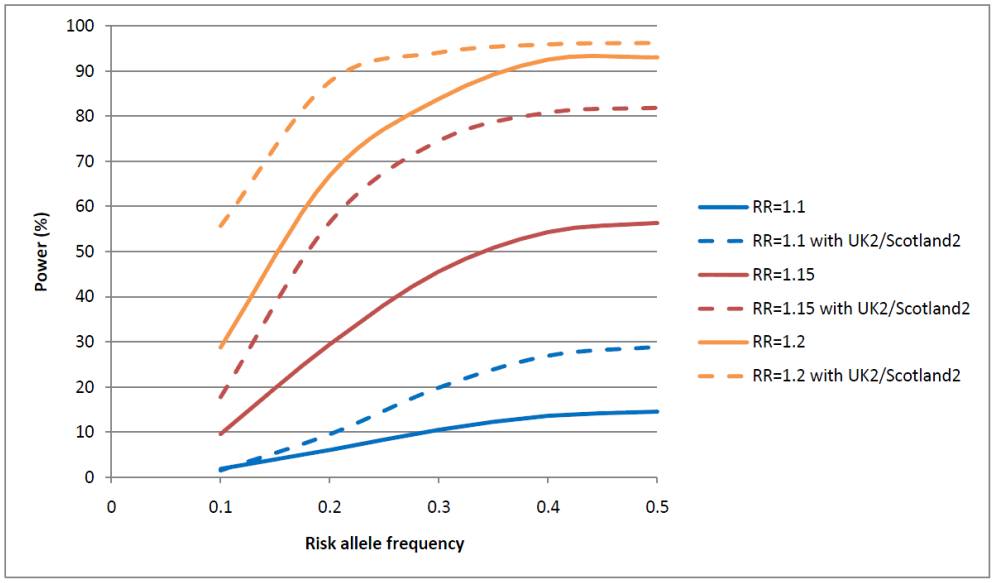
Supplementary Figure 1: Principal components analysis of VQ58, UK1/CORGI and Scotland1/COGS cohorts.

The first 2 components are shown after removal of outliers.



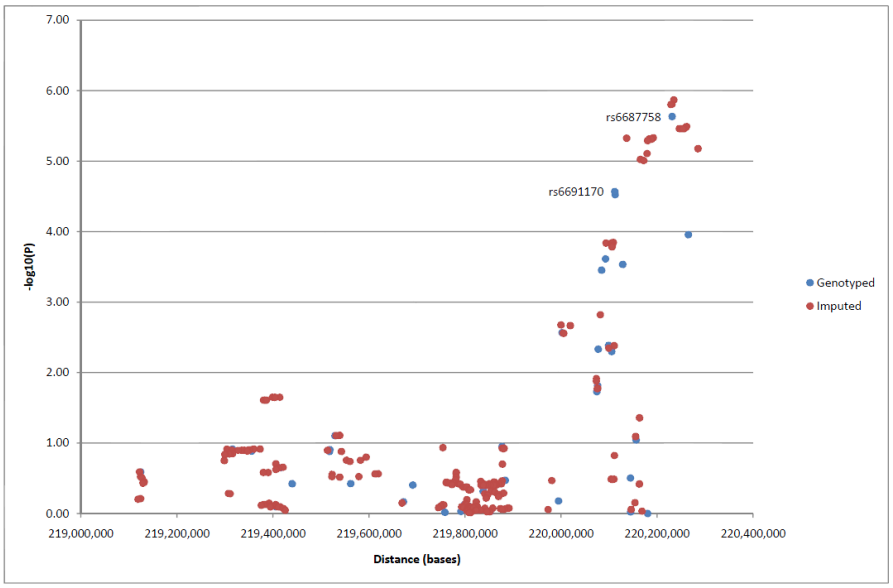
Supplementary Figure 2: Comparison of the power of the two alternative strategies: meta-analysis of VQ58+UK1+Scotland 1, or meta-analysis of VQ58+UK1+Scotland1+UK2+Scotland2.

The power calculations shown are based on illustrative scenarios under which the alternative strategies might have been performed. In strategy 1 (solid lines), meta-analysis is based on VQ58+UK1+Scotland1 and SNPs are taken for validation at a specified threshold of $P<0.00025$ (approx. top 100 SNPs). In strategy 2 (dashed lines), meta-analysis is based on VQ58+UK1+Scotland1+UK2+Scotland2 and a smaller number of SNPs is taken for validation at a threshold of $P<0.000025$ (approx. top 10 SNPs); under this latter scenario, if a SNP fell outside the top 55,000 SNPs (ranked by P) from the meta-analysis of UK1+Scotland1, it was excluded from the 5-way meta-analysis because it was not genotyped in UK2 and Scotland2. Under the scenarios presented and most other plausible scenarios, power was greater under strategy 2 (dashed lines). That strategy was also, of course, more cost-effective.

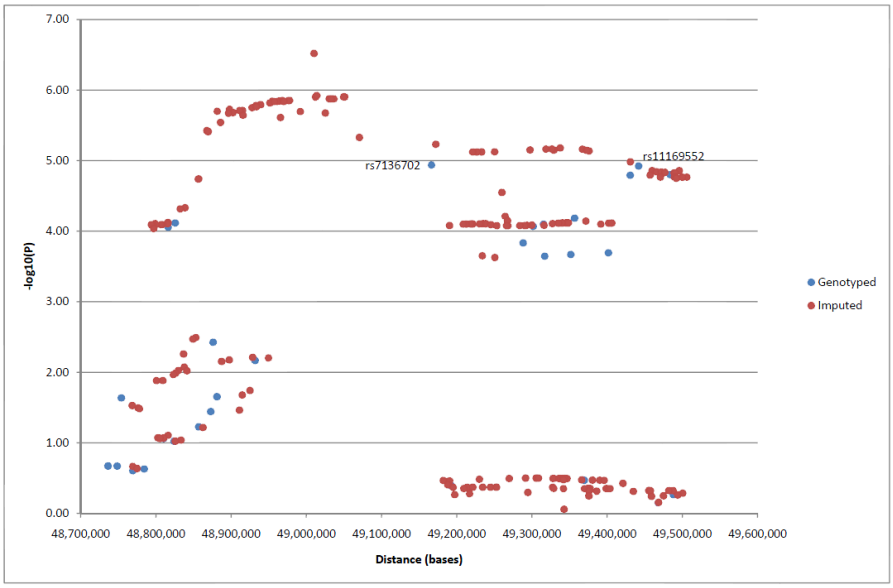


Supplementary Figure 3: The (a) 1q41 and (b) 12q13.13 regions, showing signals of association by position for genotyped (blue) and imputed (red) SNPs.

(a)



(b)



Supplementary Note

Case and control sample sets

All samples were collected with local ethical committee approval and with informed consent.

VQ58 and **COIN/NBS** are described in the main Methods.

UK1/CORGI comprised cases with colorectal neoplasia (47% male) ascertained through the Colorectal Tumour Gene Identification (CoRGI) consortium. All had at least one first-degree relative affected by CRC and one or more of the following phenotypes: CRC at age 75 or less; any colorectal adenoma (CRAd) at age 45 or less; ≥ 3 colorectal adenomas at age 75 or less; or a large (>1cm diameter) or aggressive (villous and/or severely dysplastic) adenoma at age 75 or less. Controls (45% males, 55% females) were spouses or partners unaffected by cancer and without a personal family history (to 2nd degree relative level) of colorectal neoplasia. Known dominant polyposis syndromes, HNPCC/Lynch syndrome or bi-allelic *MYH* mutation carriers were excluded. All cases and controls were of white UK ethnic origin.

UK2/NSCCG consisted of CRC cases (58% male, mean age at diagnosis 59.3 years; SD ± 8.7) ascertained through two ongoing initiatives at the Institute of Cancer Research/Royal Marsden Hospital NHS Trust (RMHNHST) from 1999 onwards - The National Study of Colorectal Cancer Genetics (NSCCG) and the Royal Marsden Hospital Trust/Institute of Cancer Research Family History and DNA Registry. Controls (41% males; mean age 59.8 years; SD ± 10.8) were the spouses or unrelated friends of patients with malignancies. None had a personal history of malignancy at time of ascertainment. All cases and controls had self-reported European ancestry, and there were no obvious differences in the demography of cases and controls in terms of place of residence within the UK.

Scotland1/COGS included CRC cases (51% male; mean age at diagnosis 49.6 years, SD ± 6.1) and cancer-free population controls (51% male; mean age 51.0 years; SD ± 5.9). Cases were for early age at onset (age ≤ 55 years). Known dominant polyposis syndromes, HNPCC/Lynch syndrome or bi-allelic *MYH* mutation carriers were excluded. Control subjects were sampled from the Scottish population NHS registers, matched by age (± 5 years), gender and area of residence within Scotland.

Scotland2/SOCCS comprised CRC cases (61% male; mean age at diagnosis 65.8 years, SD ± 8.4) and population controls (60% males; mean age 67.9 years, SD ± 9.0) ascertained in Scotland. Cases were taken from an independent, prospective, incident CRC case series and aged <80 years at diagnosis. Control subjects were population controls matched by age (± 5 years), gender and area of residence within Scotland.

UK3/NSCCG comprised CRC cases (66% male; mean age at diagnosis 59.1 years, SD ± 8.1) and 3,017 controls (40% male; mean age 61.7 years, SD ± 11.4) ascertained through NSCCG post-2005.

Scotland3/SOCCS comprised CRC cases (50% male; mean age at diagnosis 53.2 years, SD ± 15.4) and cancer-free population controls (47% male; mean age 51.8 years, SD ± 11.5). Controls were recruited as part of the Generation Scotland study.

UK4/CORGI2BCD consisted of CRC cases (46% male; mean age at diagnosis 58.3 years; SD ± 14.1) and NNN cancer-free population or spouse controls (45% male; mean age 45.1 years, SD ± 15.9)

Helsinki/FCCPS comprised CRC cases (53% males; mean age at diagnosis 66.9 years, SD ± 12.2) and controls (random, anonymous Finnish blood donors) ascertained in south-eastern Finland.

Cambridge/SEARCH consisted of CRC cases (56% male; mean age at diagnosis 59.2 years, SD ± 8.1) and 2,262 controls (42% males; mean age 57.6 years; SD ± 15.1. Samples were ascertained through the SEARCH (Studies of Epidemiology and Risk Factors in Cancer Heredity) study based in Cambridge, UK. Recruitment of CRC started in 2000; initial patient contact was though the general practitioner. Control samples were collected post-2003. Eligible individuals were sex- and frequency-matched in five-year age bands to cases.

Consortium members

The CORGI Consortium comprises: Eamonn Maher, Dept. of Clinical Genetics, University of Birmingham, UK; Gareth Evans, Dept. of Clinical Genetics, University of Manchester, UK; Lisa Walker and Dorothy Halliday, Oxford Regional Genetics Service, Churchill Hospital, Oxford, UK; Anneke Lucassen, Wessex Regional Genetics Service, Princess Anne Hospital, Southampton, UK; Joan Paterson, Anglia Regional Genetics Service, Addenbrooke's Hospital, Cambridge, UK; Shirley Hodgson and Tessa Homfray, South-West Thames Regional Genetics Service, St George's Hospital, Tooting, London, UK; Lucy Side, North-East Thames Regional Genetics Service, Great Ormond Street Hospital, London, UK; Louise Izatt, South-East Thames Regional Genetics Service, Guy's Hospital, London, UK; Alan Donaldson and Susan Tomkins, South-West Regional Genetics Service, Bristol, UK; Patrick Morrison, Northern Ireland Regional Genetics Service, City Hospital, Belfast, UK; Carole Brewer, South-West Regional Genetics Service, Royal Devon and Exeter Hospital, Exeter, UK; Alex Henderson, Northern Regional Genetics Service, International Centre for Life, Newcastle, UK; Rosemarie Davidson and Victoria Murday, West of Scotland Regional Genetics Service, Yorkhill Hospital, Glasgow, UK; Jaqueline Cook, Sheffield Regional Genetics Service, Children's Hospital, Sheffield, UK; Neva Haites, North of Scotland Regional Genetics Service, Foresterhill Hospital, Aberdeen, UK; Timothy Bishop and Eamonn Sheridan, Yorkshire Regional Genetics Service, St James's Hospital, Leeds, UK; Andrew Green, Republic of Ireland Genetics Service, Our Lady's Hospital for Sick Children, Dublin, Republic of Ireland; Christopher Marks, Sue Carpenter and Mary Broughton, The Royal Surrey County Hospital, Egerton Road, Guildford, Surrey; Lynn Greenhalge, Department of Clinical Genetics, Royal Liverpool Children's Hospital, Eaton Road, Alderhay, Liverpool; Mohnish Suri,Department of Clinical Genetics, City Hospital, Hucknall Road, Nottingham

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