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Recurrent Coding Sequence Variation Explains Only A Small Fraction of the Genetic Architecture of Colorectal Cancer

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Whilst common genetic variation in many non-coding genomic regulatory regions are known to impart risk of colorectal cancer (CRC), much of the heritability of CRC remains unexplained. To examine the role of recurrent coding sequence variation in CRC aetiology, we genotyped 12,638 CRCs cases and 29,045 controls from six European populations. Single-variant analysis identified a coding variant (rs3184504) in *SH2B3* (12q24) associated with CRC risk ($OR = 1.08$, $P = 3.9 \times 10^{-7}$), and novel damaging coding variants in 3 genes previously tagged by GWAS efforts; rs16888728 (8q24) in *UTP23* ($OR = 1.15$, $P = 1.4 \times 10^{-7}$); rs6580742 and rs12303082 (12q13) in *FAM186A* ($OR = 1.11$, $P = 1.2 \times 10^{-7}$ and $OR = 1.09$, $P = 7.4 \times 10^{-8}$); rs1129406 (12q13) in *ATF1* ($OR = 1.11$, $P = 8.3 \times 10^{-9}$), all reaching exome-wide significance levels. Gene based tests identified associations between CRC and *PCDHGA* genes ($P < 2.90 \times 10^{-6}$). We found an excess of rare, damaging variants in base-excision ($P = 2.4 \times 10^{-4}$) and DNA mismatch repair genes ($P = 6.1 \times 10^{-4}$) consistent with a *recessive* mode of inheritance. This study comprehensively explores the contribution of coding sequence variation to CRC risk, identifying associations with coding variation in 4 genes and *PCDHG* gene cluster and several candidate recessive alleles. However, these findings suggest that recurrent, low-frequency coding variants account for a minority of the unexplained heritability of CRC.

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Heritable factors are thought to contribute to around 35% of the variation in risk of developing colorectal Cancer (CRC)[1–3]. High-penetrance mutations responsible for Mendelian disorders such as Lynch Syndrome, familial adenomatous polyposis and MUTYH associated polyposis have been shown to account for around 5% of all CRC. Genome-wide association studies (GWAS) have vindicated the notion that common genetic variants also contribute to CRC risk. Over 25 risk SNPs identified through GWAS[4–15] are collectively responsible for only around 1% of CRC heritability[3] and so much of the genetic contribution to CRC risk currently remains enigmatic. It has been proposed that low frequency variants in coding regions, may have substantial effects on risk and so may explain an appreciable proportion of the heritability of complex disease[16]. Conventional GWAS arrays have been sub-optimally configured to genotype such low frequency recurrent variation, whilst large-scale sequencing has been constrained by cost and data analysis bottlenecks.

Exome sequencing studies in multiple populations have enabled the assembly of catalogues of well-characterised single nucleotide variants within the coding sequence of genes. Genotyping arrays have been formatted into "exon" arrays specifically designed to interrogate recurrent genetic variation with putative impact on gene function. We set out to test the hypothesis that variation within gene coding sequences is associated with CRC risk, by making use of the recently introduced Illumina Exon array.

Results

Post QC exome-wide analysis was based on 8,100 CRC cases and 21,820 controls from the six case-control series (Supplementary Tables 1 and 2). We also made use of genotypes for ~10,000 SNPs (~54% variants are non-synonymous) that were included in our previously published GWASs[8,10], thus increasing power and providing additional exome array variant data on 4538 cases and 7225 controls (Supplementary Methods, Supplementary Table 3). Prior to the meta-analysis, we assessed the adequacy of the case-control matching and possibility of differential genotyping of cases and controls in individual studies using Quantile-Quantile (Q-Q) plots of test statistics (Supplementary Figure 6). Using data from the above 9 case-control series, we derived for each SNP joint odds ratios (ORs) and confidence intervals (CIs) in a meta-analysis under a fixed-effects model and determined the associated P values. Overall 72,162 non-monomorphic post-QC variants observed in at least 2 studies contributed to the combined meta-analysis totalling 12,638 cases and 29,046 controls (Supplementary Table 1). Of these variants, 29,117 variants were rare ($MAF < 1\%$) and 32,809 variants exhibited $MAF < 5\%$. We found no appreciable inflation of test statistics for the meta-analysis as a whole, $\lambda_{90\%bottom} = 0.98$, thereby excluding significant differential genotyping or cryptic population substructure (See Q-Q plot in Supplementary Figure 7)[8,10,13].

SNP rsID	Gene	Annota-tion	CHR	BP	Risk Allele	Reference Allele	EAF (cases/controls)	N studies	N cases	N controls	OR	P value	P value Bonferroni adjusted
rs1129406	*ATF1*	coding-synon	12	51203371	A	G	0.43/ 0.40	6	4730	12603	1.11	8.30×10^{-9}	7.44×10^{-04}
rs12303082	*FA-M186A*	missense	12	50754563	A	C	037/0.35	9	10207	19886	1.09	7.40×10^{-8}	6.63×10^{-03}
rs6580742	*FA-M186A*	missense	12	50727811	A	G	0.20/0.19	9	12539	29208	1.11	1.20×10^{-7}	0.01
rs16888728	*UTP23*	missense	8	117783975	A	G	0.11/0.10	8	10621	26779	1.15	1.40×10^{-7}	0.01
rs3184504	*SH2B3*	missense	12	111884608	G	A	0.53/0.51	9	12530	29197	1.08	3.90×10^{-7}	0.03

Table 1. Results of meta-analysis for variants reaching exome-wide level of significance (4×10^{-7}) under a fixed effects model. EAF – effect allele frequency.

Single variant analysis. 17 variants showed evidence for an association with CRC which exceeded Bonferroni-corrected exome-wide threshold of statistical significance (Table 1, Supplementary Table 4, Supplementary Figure 7), 4 of these 17 variants were non-synonymous missense variants: (rs3184504 (p.Trp263Arg) in *SH2B3* (12q24; OR = 1.08, $P = 3.9 \times 10^{-7}$, effect allele frequency (EAF) = 0.52); rs16888728 (p.Pro215Gln) in *UTP23* (8q24; OR = 1.15, $P = 1.4 \times 10^{-7}$, EAF = 0.10); two variants in *FAM186A* (12q13) - rs6580742 (p.Met2193Ile, OR = 1.11, $P = 1.2 \times 10^{-7}$, EAF = 0.19) and rs12303082 (p.Lys187Gln, OR = 1.09, $P = 7.4 \times 10^{-8}$, EAF = 0.36)). Another variant within 12q13 loci rs1129406 (12q13; OR = 1.11 $P = 8.3 \times 10^{-9}$, EAF = 0.41) is located within a splice region of *ATF1*. The rs3184504 association highlights a novel CRC risk locus (Table 1, Supplementary Figure 8). The p.Trp263Arg amino acid change resides in exon 3 of the SH2B adaptor protein and is predicted to be benign and tolerated by PolyPhen[17] and SIFT[18]. Though predicted to be located within a transcription factor binding site (*POLR2A*) in lymphoblastoid, leukaemia and glioblastoma cell lines, it seems unlikely affect binding according to RegulomeDB (score 3a)[19] or influence expression of *SH2B3* in lymphoblastoid cell lines[20,21] and other tissues[22,23]. Conditional analysis showed that rs3184504 genotype was sufficient to explain all of the effect at the 12q24 risk locus (Supplementary Table 5).

The 4 other novel SNPs rs16888728, rs6580742, rs12303082 and rs1129406 map to the previously described 8q24.11[12,24] and 12q13.12 loci[10] (Table 1). rs16888728 is located within exon 3 of *UTP23* (8q23.3, 117783975, p.Pro215Gln) and is in moderate linkage disequilibrium (LD) with rs16892766 (8q23.3, 117630683)[24] (D' = 0.63, $r^2 = 0.30$). Mutual adjustment was unable to distinguish the effects of rs16888728 on CRC risk from the previously described GWAS association, suggesting rs16892766 to be a primary signal (rs16888728, $OR_{cond} = 0.99$, $P_{cond} = 0.83$; rs16892766, $OR_{cond} = 1.27$, $P_{cond} = 5.3 \times 10^{-10}$) (Supplementary Table 6).

Detailed analysis of the 12q13 locus encompassing coding variants in *ATF1* and *FAM186A* showed that three new variants are within a region of fairly extensive linkage disequilibrium (LD) ($r^2 = 0.31–0.68$, D' = 0.92–1) and in moderate LD with rs11169552, a previously identified through GWAS[10] CRC risk locus ($r^2 = 0.08 – 0.24$, D' = 0.95–0.99). Both rs6580742 and rs12303082 are missense variants located within the exon 1 (rs6580742, chr12:50727811, p.Met2193Ile) and exon 3 (rs12303082, chr12:50754563, p.Lys187Gln) of *FAM186A*. Strongest signal at the locus (rs1129406) is a synonymous coding variant in *ATF1* located within the splice region of gene, though it is unclear if the normal splicing of the gene is affected by the variant. rs6580742 is located within DNaseI hypersensitivity cluster and in eQTL with DIP2B and KIAA1463 expression in lymphoblastoid cell lines[19,25,26] and cis-eQTL with ATF1 expression in esophagus mucosa, subcutaneous adipose tissue, tibial artery[22,23]. It is likely to affect binding according to RegulomeDB (score 1f)[19,27]. Conditional analyses indicate that all the association signals, including previously identified rs11169552[10] (OR = 1.08, $P = 2.55 \times 10^{-5}$, $OR_{cond} = 1.02$, $P_{cond} = 0.35$,EAF = 0.73), are explained by rs1129406, the splice region variant in *ATF1* (Supplementary Table 7).

The remaining 10 SNPs in non-coding regions had been identified through our previous GWAS studies of CRC[10,11,13,28–30]. We subsequently applied conditional analysis to interrogate all CRC risk loci highlighted by the current study but found no evidence of multiple signals at 1q41, 8q24.21, 15q13.3, 18q21.1, 19q13.11, 20p12.3 and 20q13.33 (Supplementary Tables 8–14).

We further explored if rs1129406 (*ATF1*, 12q13), rs12303082 (*FAM186A*, 12q13), rs6580742 (*FAM186A*, 12q13), rs16888728 (*UTP23*, 8q24) and rs3184504 (*SH2B3*, 12q24) genotypes affect the CRC risk differentially by sex, age at diagnosis, tumor site, stage and MSI status (Supplementary Table 15). Intriguingly, we found that rs16888728 is significantly associated with gender in case-only analysis (OR = 1.21, $P = 5.6 \times ^{-4}$) with no effect on CRC risk in males in case-control analysis (OR = 1.28, $P = 5 \times 10^{-8}$ in women and OR = 1.06 and P = 0.14 in men).

Gene-based analysis. Following on from these single variant analyses we conducted a gene-based analysis for rare (MAF < 1%) and low-frequency (MAF < 5%) variants observed in at least two cohorts (Supplementary Figure 9, Table 2). Meta-analysis of SKAT-O results showed some evidence of inflation

SetID	Gene	N of variants #	Description	Chr	band	p.value
(A) low frequency (MAF < 5%) variants (n = 16,585)						
ENSG00000254245	*PCDHGA3*	89	protocadherin gamma subfamily A, 3	5	q31.3	7.29E-07
ENSG00000081853	*PCDHGA2*	90	protocadherin gamma subfamily A, 2	5	q31.3	7.49E-07
ENSG00000204956	*PCDHGA1*	91	protocadherin gamma subfamily A, 1	5	q31.3	7.86E-07
ENSG00000254221	*PCDHGB1*	82	protocadherin gamma subfamily B, 1	5	q31.3	1.43E-06
ENSG00000262576	*PCDHGA4*	79	protocadherin gamma subfamily A, 4	5	q31.3	2.91E-06
(B) High and Moderate low frequency (MAF < 5%) variants (n = 16,081)						
ENSG00000254245	*PCDHGA3*	83	protocadherin gamma subfamily A, 3	5	q31.3	2.59E-06
ENSG00000081853	*PCDHGA2*	84	protocadherin gamma subfamily A, 2	5	q31.3	2.79E-06
ENSG00000204956	*PCDHGA1*	85	protocadherin gamma subfamily A, 1	5	q31.3	2.96E-06

Table 2. Meta-analysis of gene-based (SKAT-O) tests. Top significant results for SKAT-O gene-based test for different subsets. We used Bonferroni correction to identify Exome-Wide level of significance for each of the subgroup separately. Only variants, which were observed in at least two independant studies, were included in the analysis. Genes with less than 2 variants per gene were exluded. Variants were defined High and Moderate accordind to classification adapted by SnpEff. # N of variants is based by the number of SNPs located within the genes and may vary by study, e.g. in case of monomorphic alleles.

($\lambda = 1.45$ in analysis for low –frequency variants). Among the genes showing evidence of association in low-frequency variants analysis were tandemly located genes from protocadherin gamma gene cluster (*PCDHGA3, PCDHGA2, PCDHGA1, PCDHGA4, PCDHGB1*, 5q31.3, $P < 2.9 \times 10^{-6}$). The details of the SNPs contributing to *PCDHG* associations are given in Supplementary Table 16. None of the genes reached significance in rare – variant analysis.

Gene-ontology (GO) enrichment analysis implicated homophilic cell adhesion genes in CRC development (Supplementary Table 17).

Search for candidate high-penetrance CRC alleles. Next, we searched for rare high penetrance CRC variants by analysis of rare damaging variants present in more than 3 CRC cases, but absent from controls. In the analysis of dominant alleles, we observed truncating variants in *NWD1*, *CD1A*, *ZNF594*, *DNAH9*, *ZNF418*, *ABTB1* and *HIST1H3A* and two missense variants in *GCN1L1* (Supplementary Table 18). We also assessed the contribution of rare recessive alleles present in >3 cases, but absent in controls (Supplementary Table 18). Notable among these homozygotes were stop codon (p.Tyr90*) in the base excision repair gene, *NTHL1*, as well as homozygous missense variants in the DNA mismatch-excision repair gene, *PMS1* (p.Thr75Ile) (Supplementary Figure 10). Overall we saw an excess of rare homozygous variants in base excision repair (16/8100 cases vs. 10/21820 controls, OR = 4.31; $P = 2.4 \times 10^{-4}$) and mismatch repair genes (11/8100 cases vs. 5/21820 controls, OR = 5.93, $P = 6.1 \times 10^{-4}$) in cases (Supplementary Table 19).

We also sought evidence of compound heterozygosity in cases and identified two damaging *NOTCH2* variants and three damaging variants in *DNAJC17* (DnaJ (Hsp40) homolog, subfamily C, member 17) that were observed to be present in heterozygous state at least twice in 2 and more cases, but absent in controls (Supplementary Table 20). *NOTCH2* is regulated by Wnt signalling and known to have lower expression in colorectal and ovarian cancer[31].

Discussion

We have identified coding variation in 4 genes (*SH2B3, UTP23, FAM186A*, *ATF1)* and *PCDHG* gene cluster that contribute to the risk of developing CRC. Three of the 4 genes with new coding variants influencing CRC risk had been identified by previous GWAS SNPs[10,12,24]. Novel association between the coding variant (rs3184504) in the *SH2B3* gene has been described during the process of preparation and review of this manuscript in an independent meta-analysis[32]. Perhaps the most interesting finding of this well-powered study is the observation that very few recurrent coding sequence variants contribute to CRC risk, and certainly not with major effect size (OR > 2.5).

The association between CRC risk and the adaptor protein, SH2B3, is interesting, since rs3184504 results in a predicted benign non-synonymous amino acid substitution (p.Trp263Arg) within the plekstrin homology domain of SH2B3. SH2B3 is induced upon JAK-STAT3 phosphorylation and is expressed at high levels in haematopoietic cells, but only at low levels in the normal colon. The protein is a regulator of cytokine signals at the cell surface through tyrosine kinase signalling cascades and is thought to act as a negative regulator of such signals at the cell surface to impart an anti-proliferative effect. A consanguineous family has been reported which segregates a germline frameshift mutation in the Plekstrin homology domain of SH2B3. Homozygous individuals developed various autoimmune phenotypes and one sibling developed acute lymphoblastic leukaemia (ALL) as an infant[33]. Somatic *SH2B3* mutations have also been identified in 3% of ALL, suggesting that *SH2B3* loss plays a role in initiation and progression of human leukaemia through dysregulated cytokine signalling. Interrogation of TCGA and Broad Institute sequence data from colorectal adenocarcinomas[34–36] did not identify an excess of somatic mutations in SH2B3 (0.69% of samples carry deleterious mutations or copy number variations), suggesting that SH2B3 mutations are not drivers in CRC progression[33]. Genetic variation at the SH2B3 gene locus has been associated with various autoimmune related disorders including hepatitis[37], rheumatoid arthritis[38], hypothyroidism[39], type 1 diabetes[40], vitiligo[41], rheumatoid arthritis and coeliac syndrome[42], suggesting that SH2B3 dysfunction may be involved in mediating disordered immune function and thereby play a role in cancer susceptibility. Interestingly, SH2B3 is over-expressed in ovarian tumour cells with evidence for a role in activating signal transduction[43]. SH2B3 expression status may have paradoxical effects in cancer, dependent on cellular context.

The variant in *UTP23* (rs16888728) also exerts a modest effect on CRC risk. The UTP23 transcript is expressed at modest levels in many tissue types. It has sequence homology to a yeast protein involved in ribosomal RNA processing and ribosome biogenesis. As such, it may be involved in alternative splicing, although very little is known about the functional role of the human protein. The coding variant (rs16888728) is located within exon 3 of *UTP23* and results in a non-conserved amino acid substitution (p.Pro215Gln, GERP score = −0.543). Conditional analysis was unable to distinguish the effects of rs16888728 on CRC risk from that of the previously described[24] GWAS association (rs16892766). Interrogation of tumour sequence databases reveals no significant excess of mutations in CRC (<1% prevalence)[34–36]. However, *UTP23* is amplified in ~5% of CRC tumours[35,36] with significant correlation between UTP1 mRNA expression and copy number variation.

The SNP rs1129406, a splice site variant in *ATF1*, appears to explain the association signal at the 12q13 locus, including that of a previous signal identified by GWAS (rs11169552)[10]. ATF1 is a transcription factor that, when phosphorylated, induces transcriptional transactivation of target genes. Fusion of *ATF1* with the Ewing's Sarcoma gene, or with FUS, results in continuous signaling and sarcomatous tumour formation. Common variation has not been associated with other cancers, however significant cis-eQTL with ATF1 was detected for this variant in esophagus mucosa, subcutaneous adipose tissue and tibial artery[22,23]. Whilst there are no excess of somatic mutations in CRC tissue in TCGA or Broad data, rs1129406 may be the causative variant that explains the previous GWAS signal. The relationship of *FAM186A* to CRC risk is somewhat opaque, as very little is known about this gene. *FAM186A* appears to be a protein coding gene, rather than a lncRNA. Hence we cannot exclude the possibility that the effect is mediated through regulatory effects.

The gene-based test, SKAT-O, highlighted several genes from protocadherin gamma (PCDHG) gene cluster on chromosome 5 exhibiting a composite excess of coding variants and thereby indicating the gene is associated with CRC risk. Somatic genomic missense and nonsense mutations in one of the identified genes are present in 11.8% of CRC cases and up to 31% of all skin cuteneous melanomas (according to The Cancer Genome Atlas data)[35]. PCDHG gene cluster encodes 22 genes divided into 3 subfamily (A,B and C) based on sequence similarities with multiple transcripts generated by alternative splicing[44]. PCDH expression is observed in colon and long range epigenetic silencing of PCDH cluster region has been described in Wilm's tumours[45], breast cancers[46] and colorectal adenomas and carcinomas[47]. Hence, PCDH genes play role of tumour suppressor and silencing mutations might be expected to have tumour-promoting effects. Whilst PCDHG cluster genes are strong candidates based on the analysis presented in this study, further work is required to confirm the role of these genes in cancer predisposition.

The identification of damaging alleles acting as rare recessive traits in genes that participate in DNA repair, with known paradigms in CRC susceptibility, such as *NTHL1* (p.Tyr90*) and *PMS1* (p.Thr75Ile) clearly require further study as these represent strong candidate recessive alleles. Recently *NTHL1* loss-of-function germline mutation has been described in families with adenomatous polyposis and progression to CRC inherited in recessive mode[48], thus suggesting that the observed association is real and our search for rare damaging alleles is a successful approach to identify candidate variants. The observed excess of rare damaging variants in base-excision and mismatch repair genes suggests that the clinical importance of moderately penetrant, disease-causing, variants in DNA repair genes may be underestimated. However, further studies will require even larger sample sizes, given the rarity of the alleles, unless sequencing can identify new alleles in addition to those catalogued here. Indeed, many of the genes with damaging variants represent strong candidates for validation in exome and whole genome sequencing efforts.

Given the expectation that uncommon functional variation might be associated with CRC risk, with larger effect size than common variation, it is surprising that we have identified so few new coding sequence variants, and that all of these exert modest effect sizes (OR 1.08–1.15). In a linear-mixed model analysis (Supplementary Material), we estimated that the genetic variants identified though previous GWAS and significant in our meta-analysis explain approximately $1.5 \pm 0.7\%$ of the total phenotypic variance on the liability scale, while the newly identified variants account for only 0.4% of the total variance.

The Infinium Human Exome BeadChip 12v1.0 or 12v1.1 (Illumina Inc.) array was configured to identify coding sequence variants most likely to have functional consequences. Despite of its attractiveness as a cheap alternative to exome sequencing, exome array has some limitations and is not able to offer complete whole exome coverage of all possible functional variants and indels. Importantly, exome array was designed based on exome sequencing of 12,000 samples and enriched for multiple outcomes such as cardiovascular disease, obesity, diabetes, autism and cancer[49], which may not be representative of our cohorts. There were some differences in the genotyping quality between various versions of arrays used in the analyses and many variants did not pass stringent quality control criteria. Around 70,000 SNPs were non-monomorphic in European populations, present in at least two studies and passed our QC measures.

The focus on genetic variants with potential detrimental functional consequences should also enhance the *a priori* likelihood of pathogenicity. Though limited in detection of indels with only 136 present on the chip, the study was well powered to detect plausible effect sizes and allele frequencies (Supplementary Figure 11). Indeed, the study size had 80% power to detect an $OR > 3$ provided the MAF was >0.001 and an OR odds >1.8 if the MAF was 0.005. Whilst larger studies and/or meta-analysis might identify further coding variants with functional effects, the paucity of findings of recurrent low frequency coding variation impacting on CRC risk is intriguing. Because the causative gene mutations have been characterised for almost all dominant high penetrance CRC families, it seems unlikely that rare recurrent alleles in European populations have yet to be identified with large effects ($OR > 5$), apart from private mutations or recessive traits that are unlikely to be discovered through designed commercial arrays. Hence, population-specific custom exome arrays as well exome and genome sequencing of trios and families may be a way forward to identify recurrent rare genetic variation of moderate effect of risk and private mutations.

Materials and Methods

Study populations. The study was based on six independent case control series from European populations including Scotland (3,616 cases and 10,312 controls), England (4,558 cases and 11,249 controls), Germany (284 cases and 1,100 controls), Holland (480 cases and 480 controls), Spain (300 cases and 300 controls) and Portugal (200 cases and 200 controls). Details regarding these participating studies are described in the Supplementary Data (available online). All cases had histologically confirmed adenocarcinoma of the colon or rectum (codes 153 or 154 International Classification of Diseases (ICD), 9th revision or ICD10 C18, C19 or C20 codes). The study was undertaken at participating centres with written informed consent in accordance with respective Institutional Review Boards (IRB)/Ethics Committees.

To enhance our power we made use of previously published GWASs[8,10] thus providing ~10.000 exome array variant data on 3,549 cases and 3,698 controls from UK1 and UK2 studies, 3,158 cases and 3,073 controls from Scotland Phase1, Scotland Phase2 and Scotland Phase3, and 1,794 cases and 2,686 controls from the VQ58 study[8,13] (Supplementary Methods, Supplementary Tables 2, 3). After quality control and exclusion of expected and unexpected duplicates between studies we ended up with exome array variant data on 3,033 cases and 3,690 controls from UK1 and UK2 studies, 556 cases and 2,997 controls from Scotland Phase1, Scotland Phase2 and Scotland Phase3, and 949 cases and 538 controls from the VQ58 study[8,13]. Study details, details of genotyping, quality control procedures, sample and SNPs exclusion for these GWAS-focussed studies have been published previously[8] (Supplementary Data, Supplementary Tables 2, 3).

Exome Array Genotyping and Quality Control. DNA was extracted from EDTA-venous blood samples using standard methodologies at each centre. Genotyping was performed using the Infinium Human Exome BeadChip 12v1.0 or 12v1.1 (Illumina Inc., San Diego, CA), with genotype calling using Illumina GenCall for HumanExome-12v1.0 and HumanExome-12v1.1 versions called separately. Generation Scotland controls and a subset of the cases from the SOCCS study were genotyped using OmniExpressExome BeadChip 8v1.1 or 8v1.2[50] (Illumina Inc., San Diego, CA). A summary of the array SNP content[51,52] and the respective SNP inventory[53] have been provided previously. Standard quality procedure were applied, with further details of sample and probe exclusion in Supplementary Material and Supplementary Table 2. We compared MAF and genotyping call genotyping call rates between different version of arrays used in the current study and excluded all variants that showed some evidence of differences (Supplementary Figures 1,3). Additionally, we compared allele frequency to the 1000G data and UK exome array consortium (Supplementary Figure 2). Following standard quality-assurance and quality control measures this collaborative initiative provided information on 12,638 CRCs cases and 29,045 controls (Supplementary Table 1).

Statistical analysis. We designed the study according to an estimate of the sample size required to detect plausible effect sizes (OR = 1.5–5.0) at various rare allele frequencies (>0.001). Following completion of the study and all QC measures, we re-estimated statistical power for a given sample size using QUANTO version 1.2.4[54] for the main effect of genetic variant and the log-additive model of inheritance stipulating a *P*-value of 5.5×10^{-7}, which corresponds to Bonferroni-corrected exome-wide level of significance.

The association between individual variants and risk of CRC was evaluated in initial data analysis using unconditional logistic regression under a log-additive model of inheritance for each study separately. To examine whether associations at each identified locus were independent, we conducted conditional analysis by controlling for allelic dosage for the most significantly associated SNP at the locus. We subsequently applied conditional analysis to interrogate following CRC risk loci highlighted by the current study: 1q41 controlling for rs6687758, 8q23.3 controlling for rs16892766 and/or rs16888728, 8q24.21 controlling for rs10505477, rs6983267 and/or rs7014346, 11q32.1 controlling for rs3802842, 12q13.12 controlling for rs6580742, rs12303082 and rs1129406, 12q24.12 controlling for rs3184504, 14q22.2 controlling for rs4444235, 15q13.3 controlling for rs4779584, 18q21.1 controlling for rs4939827, 19q13.11 controlling for rs10411210, 20p12.3 controlling for rs961253 and 20q13.33 controlling for rs4925386.

Individual study effect estimates (Odds ratios (OR) and associated 95% confidence intervals (CIs)) derived from logistic regression were combined in a meta-analysis. We used a fixed effect inverse variance weighting model for meta-analysis to maximize discovery power of the current study[55]. Only non-monomorphic variants observed in at least two studies were included in the meta-analysis. We tested for over-dispersion of *P*-values in the meta-analysis by generating quantile-quantile (QQ) plots and deriving an inflation factor (λ). Cochran's Q statistic was used to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity. I^2 values ≥ 75% were considered to indicate excessive heterogeneity[56] and variants displaying I^2 values > 75% in were excluded from further analysis. Taking all the above measures into account, 72,162 SNPs remained in the analysis, equating to a Bonferroni-corrected exome-wide threshold of statistical significance of 5.55×10^{-7}. This is conservative given the likely linkage disequilibrium between some variants. We further examined top variants and excluded those that showed obvious problems with clustering and differences in clustering between versions of genotyping platforms in our analysis. This included monomorphic rs1058065 (exm2255298).

Association by sex, age, stage (invasive, non-invasive), MSI status and tumour site (rectal [ICD9:154], colonic [ICD9:153]) for the top new variants were further explored using ordered logistic regression in case-only analysis. All statistical tests were two-sided.

Gene based and pathway analysis. To explore the effects of more than one variant in the same gene on CRC risk, we used the small-sample-adjusted unified test, SKAT-O[57] with default weight on rare variants. All variants observed in at least two studies contributed to the SKAT-O results. We performed analyses for rare (MAF > 1%) and low frequency variants (MAF below 5%) including all and only High and Moderate effects as annotated by SnpEff [58]. Due to the different number of variants in each individual study we performed SKAT-O test separately for each individual study and combined summary statistics from individual SKAT results in a meta-analysis using "MetaSKAT" package in R[59] Similarly to single-variant analysis we tested for over-dispersion of *P*-values by generating QQ plots and deriving an inflation factor (λ). To account for multiple testing in these gene-based tests, we set the significance threshold to be $P < 2 \times 10^{-6}$ to reflect Bonferroni correction for the 23,280 genes examined. These 23,280 genes were selected on the base of the presence of 2 and more variants per gene and unique mapping coordinates. We further examined top genes and excluded those that were driven by single variant with the differences in clustering between versions of genotyping platforms in our analysis. This included monomorphic rs1058065 (*EIF2B4*) .

Further, we investigated variants contributing to the gene-based test. To determine whether genes identified in SKAT-O were enriched for particular molecular pathways, we performed a gene ontology (GO) enrichment analysis on a sorted by p value list of genes , using **G**ene **O**ntology en**RI**chment ana**L**ysis and visua**L**iz**A**tion tool (GOrilla)[60,61].

Search for candidate high-penetrance CRC alleles. We considered the possibility that rare damaging variants represented on the exome array might confer high-penetrance susceptibility to CRC and conducted exploratory data analysis. We reasoned on the basis of pre-existing empiric data that any dominant alleles would be likely to have frequencies of <0.1%, whereas recessive alleles would have frequencies of <2% in controls. Dominant alleles were filtered from the entire variant set as follows: [1] predicted not to be benign/tolerated by both SIFT[18] and PolyPhen2[17] or nonsense variants; [2] excluded probable miscalled SNPs through visual inspection of genotyping clusters; [3] absent in controls to ensure inclusion of potentially high penetrance risk alleles. Recessive alleles were filtered from the entire variant set as follows: [1] predicted not benign or tolerated by both SIFT[18] and PolyPhen2[17]; [2] excluded probable miscalled SNPs through visual inspection of genotyping; [3] homozygotes absent in controls to ensure inclusion of potentially high penetrance risk alleles; [4] minor allele frequency ≤ 0.02 in controls.

We evaluated effect of rare damaging variants under dominant or recessive model of inheritance using Fisher's exact test in a pooled analysis. Due to the limited number of rare damaging variants on traditional GWAS platforms, we included in the analysis case-control series genotyped using Exome Array only (8100 cases/21820 controls). We also looked for evidence of an excess of compound heterozygosity for rare damaging variants in cases compared to controls. The compound heterozygous list was filtered from the entire set of heterozygous variants as follows: (1) excluded probable miscalled SNPs through visual inspection of genotyping clusters, [2] predicted not to be benign/tolerated by both SIFT[18] and PolyPhen2[17], (3) number of rare damaging heterozygotes per gene in controls ≤ 1, (4) minor allele frequency ≤ 2% in controls. We further look for excess of rare damaging homozygous variants in DNA repair pathways by counting number of homozygous rare variants in cases and controls and testing significance by Fisher exact test. Although this study did not have power to detect such alleles by association testing or by gene burden tests, we catalogued all candidate alleles that fulfilled these criteria.

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Author Contributions

M.N.T., B.K., I.P.M.T., M.G.D. and R.S.H. contributed to writing of the manuscript. M.N.T., B.K., S.M.F., H.C., D.T.B., I.P.M.T., M.G.D. and R.S.H. conceived and designed the experiments. M.N.T., B.K., S.M.F., L.Y.O., I.P.M.T., M.G. and R.S.H. performed the experiments. M.N.T., B.K., V.S., L.Y.O., G.G., I.P.M.T., M.G.D. and R.S.H. analysed the data. M.N.T., B.K., S.M.F., N.W., C.P., V.S., A.L., M.G., L.Y.O., F.H., E.B., L.Z., S.D., L.M., E.T., P.B., A.T., G.G., C.H., A.C., I.J.D., S.E.H., E.N., J.B., G.S., R.W., D.F., H.M., D.R., C.T., J.W., M.S., A.B., H.F.A.V., F.J.H., T.W., A.F., W.L., C.S., J.H., S.B., P.P., K.H., A.F., H.W., R.H., M.P., C.P., M.T., C.R.-P., A.C., S.C.-B., A.C., H.C., D.T.B., I.P.M.T., M.G.D. and R.S.H. were involved in study design/sampling/ assembly/data collection, collation, curation and qulaity control/data analysis from case-control cohorts for respective centres. All authors reviewed the manuscript.

Additional Information

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Recurrent Coding Sequence Variation Explains Only A Small fraction of the Genetic Architecture of Colorectal Cancer

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Supplementary Methods

Exome Array Analysis

The study was undertaken at participating centres with written informed consent in accordance with respective Institutional Review Boards (IRB)/ Ethics Committees (CORGI REC 06/Q1702/99; SOCCS REC 11/SS/0109; LBC1921 LREC/1998/4/183; LBC1936 MREC/01/0/56; NSCCG REC 02/0/97, LUMC (P01-019), Groningen (MEC97/02/037f), Germany (IRB - AZ LD4-16.1/03.001, and ethics AZ A 156/03), EPICOLON (Hospital Clínic, 07/03/2000, ref. 460).

All cases had histologically confirmed adenocarcinoma of the colon or rectum (codes 153 or 154 International Classification of Diseases (ICD), 9th revision or ICD10 C18, C19 or C20 codes).

The study was based on six independent case control series. The Scottish series comprised 3,517 cases (2013 male, mean age 58yrs) from the Scottish colorectal cancer study (SOCCS)[1] and 99 cases (65 male, mean age 67 yrs) from Ninewells Hospital, Dundee and Perth Royal Infirmary collected between 1997 and 2000[2]. Cases were oversampled for familial CRC and/or early age at diagnosis. Population controls with no personal history of cancer were ascertained from four cohorts including 8,533 (3,599 male, mean age 55.4 yrs) - from Generation Scotland-Scottish Family Health Study[3,4]; 513 (211 male, mean age 79 yrs) and 1,004 (508 male, mean age 70 yrs) from the Lothian Birth Cohorts 1921 and 1936[5], respectively; and 262 Dundee controls (132 male) were recruited through the same General Practice surgeries as cases or from spouses/friends of cases [2].

The English series comprised 1,344 cases (807 male, mean age 60yrs), enriched for familial CRC, from the National Study of Colorectal Cancer Genetics (NSCCG)[6], 1,547 cases (852 male, mean age 61yrs) from the Colorectal Tumour Gene Identification Consortium (CORGI) [7] study or QUASAR2 clinical trial of adjuvant bevacizumab, 1,667 cases (981 male, mean age 67yrs) from cases from Yorkshire (Leeds General Infirmary and St James's Hospital, Harrogate District Hospital and York District Hospital) recruited between 1997 and 2000[2]. English cancer free controls comprised 5,964 individuals (3,350 male) from the UK 1958 Birth Cohort [8,9], 4,564 (2,056 male) from the Oxford Biobank, 648 healthy controls (301 male) from Leeds recruited via the same General Practice surgeries as Leeds cases or spouses/friends of cases and 73 controls (45 male) from York [2].

The Kiel series comprised 192 cases aged <50 years (92 male, mean age 44yrs). All cases were of German descent defined by parental birthplace and self-reported ethnicity. [10] None of the cases were Amsterdam or Bethesda positive or had a past history of inflammatory bowel disease. Population controls (N=1,008; 562 male, mean age 56 years, range 42-67) free of cancer at time of ascertainment were from POPGEN registry in Northern Germany [11]. The Heidelberg series included 92 cases (mean age at diagnosis 42 years) with familial or early-onset microsatellite stable (MS) CRC collected as part of the German HNPCC Consortium; all were Caucasian. The controls were 92 healthy blood donors frequency matched to cases by age and sex.

The Leiden series comprised 384 (190 males) patients with familial or early-onset CRC from the south-western part of the Netherlands, were found to have microsatellite-stable (MS) tumours. 384 controls were blood donors from the southwest region of the Netherlands. The Groningen series comprised 96 patients (36 male, mean age) who developed early-onset MS CRC. Population controls (n=96) had no-family or personal history of CRC or adenomas (46 male).

The Portuguese series comprised 200 patients with early-onset or familial CRC (109 male, mean age at diagnosis 49; SD±8.7). Fifty-four patients were Bethesda or Amsterdam criteria for Lynch syndrome but were mutation negative. Controls (109 male, mean age 49; SD±8.7) were blood donors from the Portuguese Oncology Institute of Porto.

The Spanish series were ascertained from the EPICOLON cohort: the 300 (194 male) cases that had tested negative for Lynch syndrome and were selected by (i) family history of CRC in first or second degree relatives (108 cases, aged 43-88 years), (ii) sporadic CRC diagnosed at under 60yrs (age-at diagnosis range 26-60yrs, 74 cases) , (iii) first degree relatives (FDR) with other Lynch tumours (28 cases, age at diagnosis range 63-71yrs) or , (iv) other (age-at diagnosis 71-73yrs,n=90). Controls comprised 300 cancer-free individuals from the Spanish population (163 male, aged 41-95yrs).

Genotyping Quality Control for Exome Array Analysis

Variants were excluded from analysis if call rate was < 99%, the variant deviated significantly from Hardy-Weinberg equilibrium (P<0.001) or was monomorphic in the studied population. We further examined clustering by visually assessing all top variants using Illumina Genome Studio and excluded probable miscalled SNPs through visual inspection of genotyping clusters. Sample exclusions were: genotyping success rate < 99%, abnormal heterozygosity (>3 standard deviations from mean); sex discrepancies between predicted and reposted gender (threshold of X chromosome homozygosity <30% for females and >70% for males), evidence of non- European ancestry using STRUCTURE analysis[12] or evidence of being population outlier based on principal component analysis (PCA) using EIGENSTRAT[13] or ACTA [14]. We also excluded unexpected duplicated samples and first degree relatives based on identity-by-descent (IBD) values. Further detail of sample and probe exclusion is detailed in Supplementary Table 2. Current study includes samples genotyped using different genotyping arrays and version of Illumina Exome array. We addressed this issue by performing comparison of minor allele frequencies and genotyping rates between different arrays and versions of arrays[15] (Supplementary Figures 1, 2 and 3). We excluded all variants that showed high deviation in frequencies and call rates (defined as abs(diff(array1, array2)) > 0.10) between arrays/version of arrays. It excluded additional 53,639 probes . Clustering of cases and controls by study and overall as well samples genotyped using different version of arrays were checked using principal component analyses as implemented in ACTA (Supplementary Figures 4 and 5)[14]. Genotyping quality control was evaluated using duplicate DNA samples in assays. 165 samples were genotyped on both the HumanExome-12v1.0 and HumanExome-12v1.1 arrays and genotype concordance was > 97% per pair, concordance rate was >99% for 2980 individuals overlapping between VQ58 study and England. Concordance of exome array genotypes with exome sequencing data performed on 14 samples was 99.7% for 6,451 sites. All variants are mapped and presented according to human reference sequence build 37 (GRCh37.p13).

Additional GWAS series

To enhance our power we made use of previously published GWASs[16,17], thus providing exome array variant data on 3,549 cases and 3,698 controls from UK1 and UK2 studies, 3,158 cases and 3,073 controls from Scotland Phase1, Scotland Phase2 and Scotland Phase3, and 1,794 cases and 2,686 controls from the VQ58 study[16,18]. Study details, details of genotyping, quality control procedures, sample and SNPs exclusion for these GWAS-focussed studies have been published previously[16]. Briefly, UK1[17] comprised 890 cases with CRC ascertained through (CoRGI) consortium. The 900 controls were spouses or partners unaffected by cancer and without a personal family history (to second-degree relative level) of colorectal neoplasia. UK2 (NSCCG) consisted of 2,659 cases ascertained through the Institute of Cancer Research /Royal Marsden Hospital NHS Trust (RMHNHST) from 1999 onwards – The NSCCG[6] and The Royal Marsden Hospital Trust/Institute of Cancer Research Family History and DNA Registry. The 2,798 controls were the cancer-free spouses or unrelated friends of cancer patients. Scotland Phase 1 (COGS)[17] comprised 973 early-onset CRC cases and 998 cancer-free population controls. An additional 178 individuals from Scotland Phase 3 study were recruited as part of SOCCS/COGS studies [18] and genotyped using Illumina HumanOmni5-4v1 array. Scotland Phase 2 was based on an additional 2,007 cases from SOCCS and 2,075 controls. VQ58 comprised 1,794 CRC cases from the VICTOR [19] and QUASAR2 (www.octo-oxford.org.uk/alltrials/trials/q2.html) trials. Controls were 2,686 individuals genotyped by the Wellcome Trust Case – Control Consortium 2 (WTCCC2) 1958 birth cohort [8]. Controls from the WTCCC2 1958 birth cohort were split and used as controls for cases from the Exome-Wide association study in UK and for cases from VICTOR/QUASAR2 trials.

VQ, UK1, Scotland Phase 1 cohorts were genotyped using Illumina Hap300, Hap240S, Hap370 or Hap550 arrays. 1958BC genotyping was performed as part of the WTCCC2 study on Hap1.2M-Duo Custom arrays. Scotland Phase 2 and UK2 samples were genotyped using Illumina Infinium-iSelect and GoldenGate arrays for a common set of 43,140 SNPs [16]. We excluded all expected duplicates between Scotland, UK and VQ58 GWAS studies and exome-array studies from Scotland and England, as well as the 1958 birth cohort controls. IBD analysis was performed across all samples and any further, unexpected, duplicates and first-degree relatives were excluded (Supplementary Table 3). After quality control procedures we ended up with ~10,000 exome array variants on 3,033 cases and 3,690 controls from UK1 and UK2 studies, 556 cases and 2,997 controls from Scotland Phase1, Scotland Phase2 and Scotland Phase3, and 949 cases and 538 controls from the VQ58 study[16,18].

Heritability analyses.

To estimate the contribution of exome-wide significant SNPs to the variance explained, we used the method proposed by Yang *et al*.[20,21], and implemented in Genome-Wide Complex Trait Analysis (GCTA) software[22]. The genetic relationship matrix was estimated from the exome array data using (1) all SNPs significant at the exome-wide level in our analysis and (2) 5 newly described variants significant at the exome-wide level. We used restricted maximum likelihood (REML), the default option for GCTA, to fit the appropriate variance components model. The final estimate of heritability on the underlying liability scale assumed that the lifetime risk of colorectal cancer was 0.06 [23].

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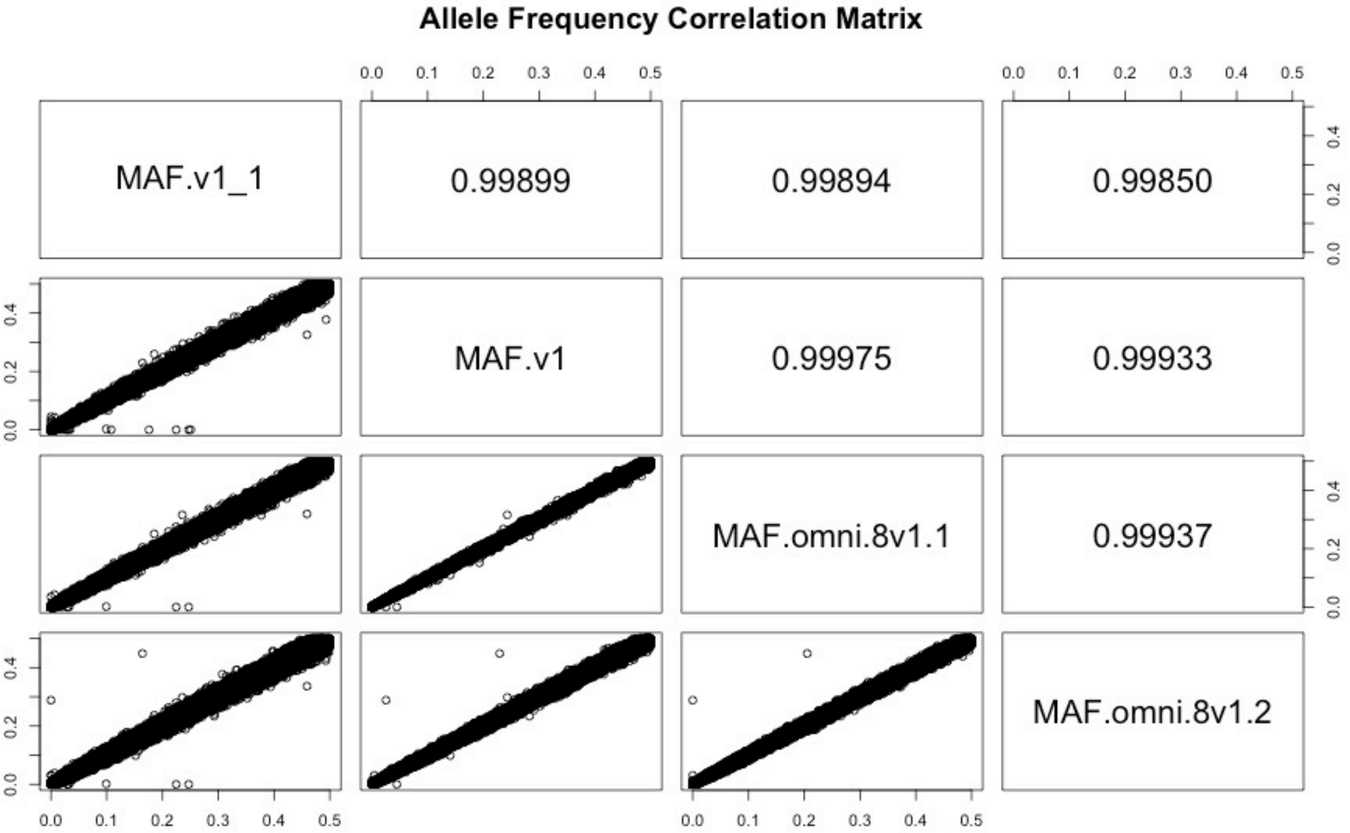
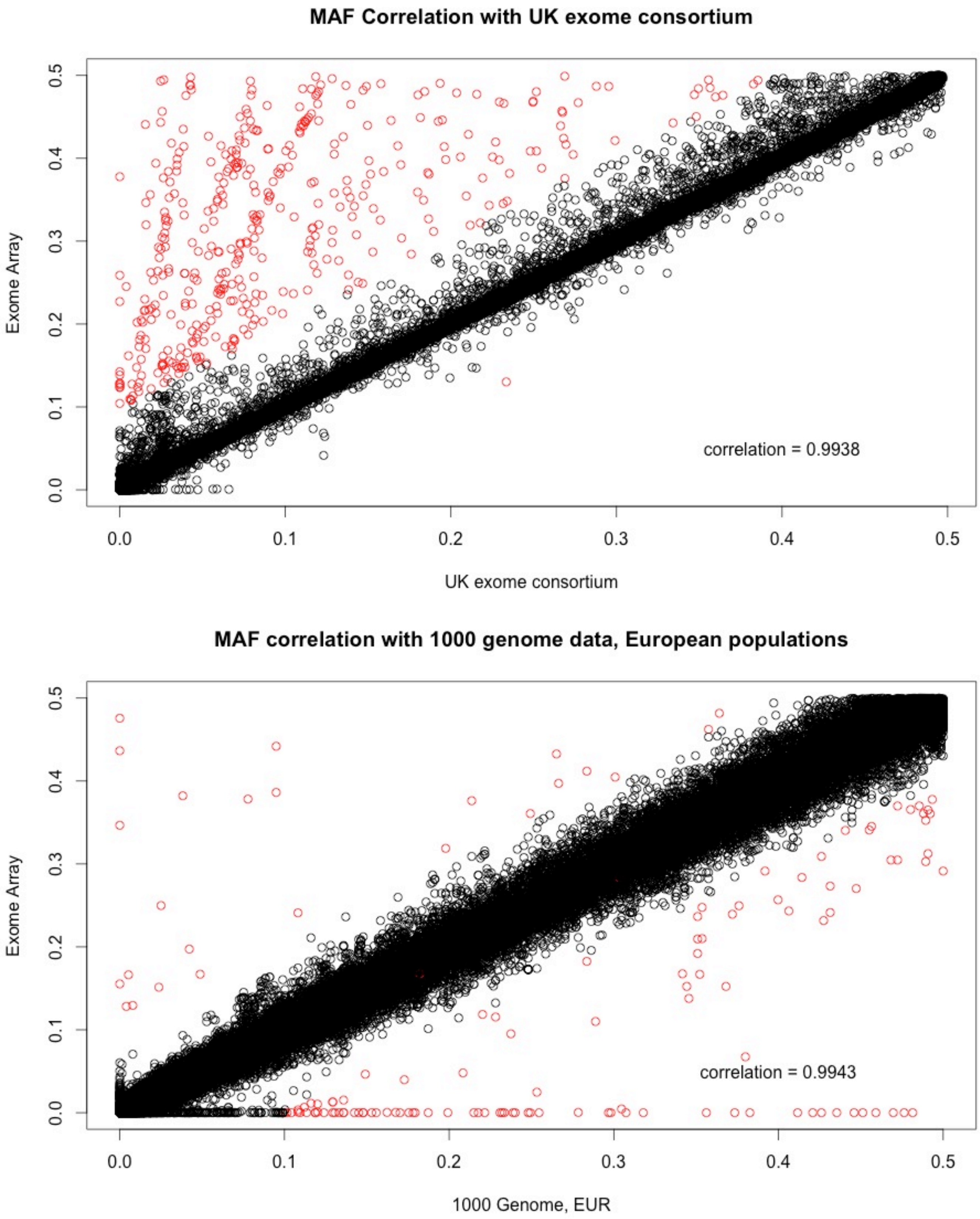
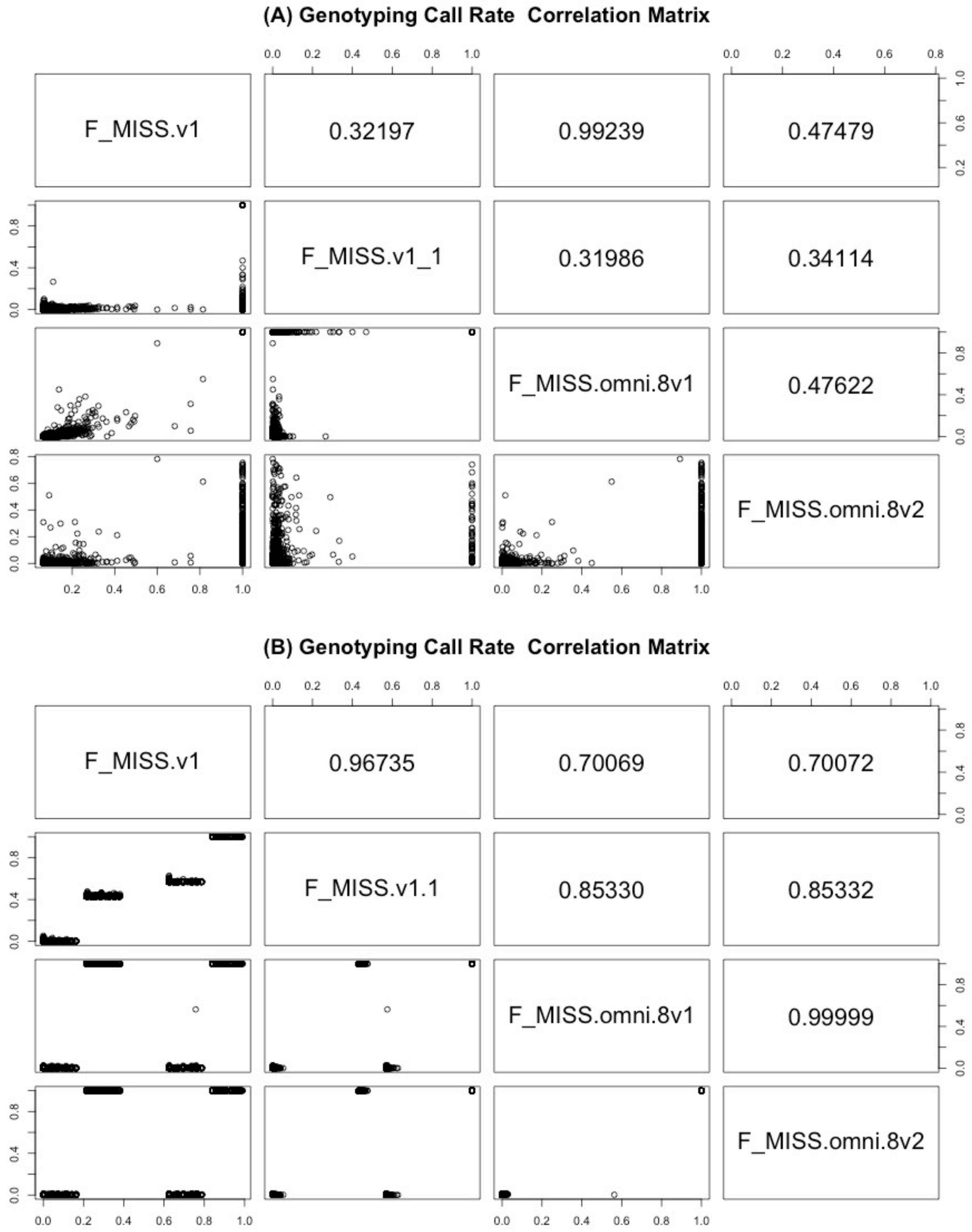


Supplementary Figure 1: Correlation matrix of allele frequency consistency between Infinium Human Exome BeadChip 12v1.0, 12v1.1 versions of arrays and OmniExpressExome BeadChip 8v1.1 / 8v1.2. MAF.v1_1 – Exome BeadChio 12v1.1 , MAF.v1 – ExomeBeadChip 12.v1.0 , MAF.omni .8v1.1 – OmniExpressExome BeadChip 8v1.1, MAF.omn.8v1.2 - OmniExpressExome BeadChip . Pearson moment correlation was calculated for each pair of comparison

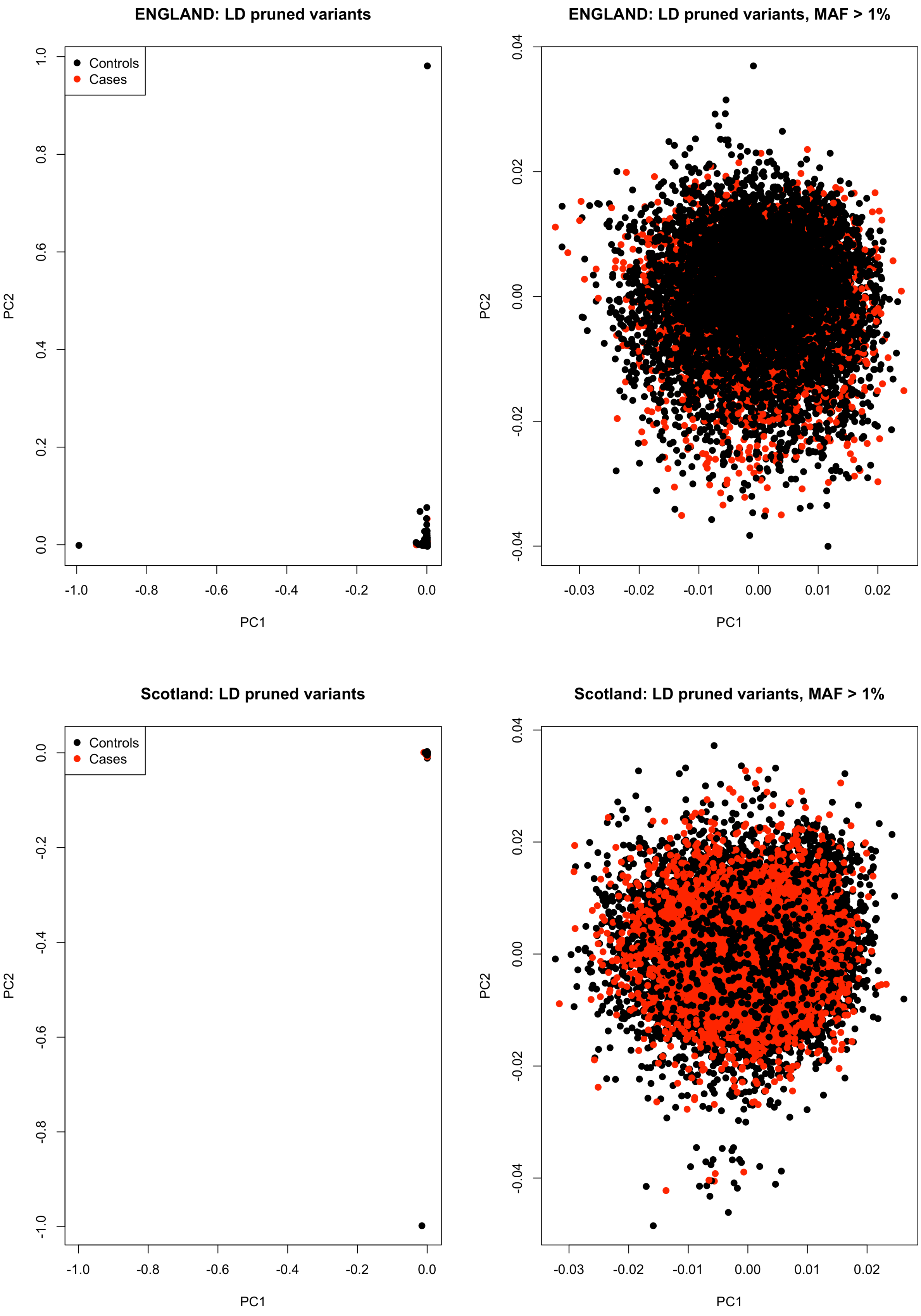


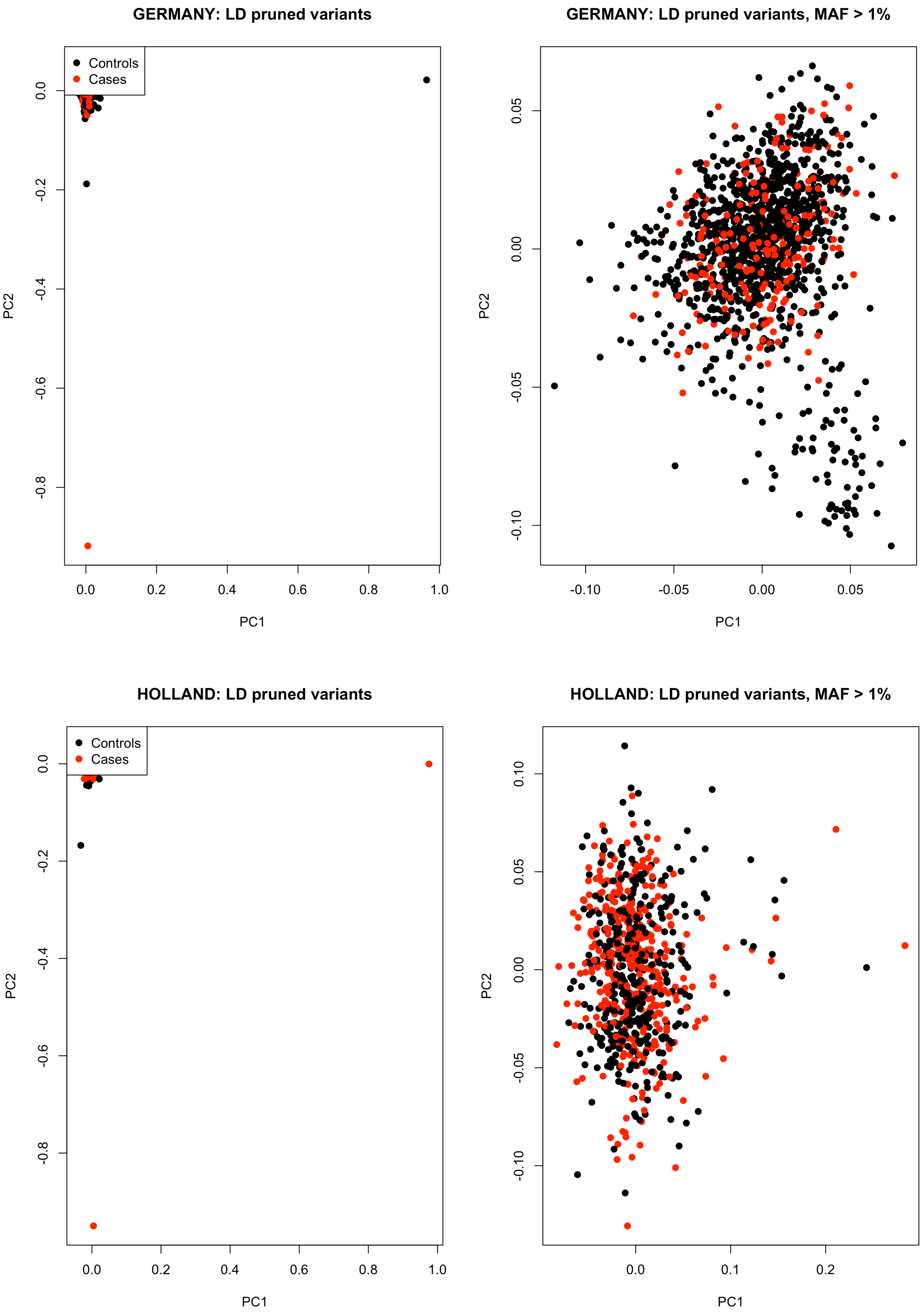
Supplementary Figure 2 Correlation of MAF between exome array project (all studies and arrays combined) and (A) frequency of Exome array variants from UK exome consortium and (B) overlapping variants in 1000 Genome data. Frequencies in UK exome consortium are calculated using 55,726 European individuals from UK (unpublished data), This set includes control individuals from Oxford BioBank, 1958 birth cohort, as well as 1843 cases from Scotland and 1209 cases from England . MAF in 1000 Genome data was calculated using information on 379 individuals of European ancestry. Correlation between allele frequencies was estimated using Pearson product-moment correlation coefficient



Supplementary Figure 3 Correlation matrix of genotyping missing rate consistency (A) prior and (B) post quality control procedures between Infinium Human Exome BeadChip 12v1.0, 12v1.1 versions of arrays and OmniExpressExome BeadChip 8v1.1 / 8v1.2.

MAF.v1_1 – Exome BeadChio 12v1.1 , MAF.v1 – ExomeBeadChip 12.v1.0 , MAF.omni .8v1.1 – OmniExpressExome BeadChip 8v1.1, MAF.omn.8v1.2 - OmniExpressExome BeadChip


ENGLAND: LD pruned variants
Controls
Cases
PC2
1.0
0.8
0.6
0.4
0.2
0.0
PC1
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
ENGLAND: LD pruned variants, MAF > 1%
PC2
0.04
0.02
0.00
-0.02
-0.04
PC1
-0.03
-0.02
-0.01
0.00
0.01
0.02
Scotland: LD pruned variants
Controls
Cases
PC2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
PC1
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
Scotland: LD pruned variants, MAF > 1%
PC2
0.04
0.02
0.00
-0.02
-0.04
PC1
-0.03
-0.02
-0.01
0.00
0.01
0.02

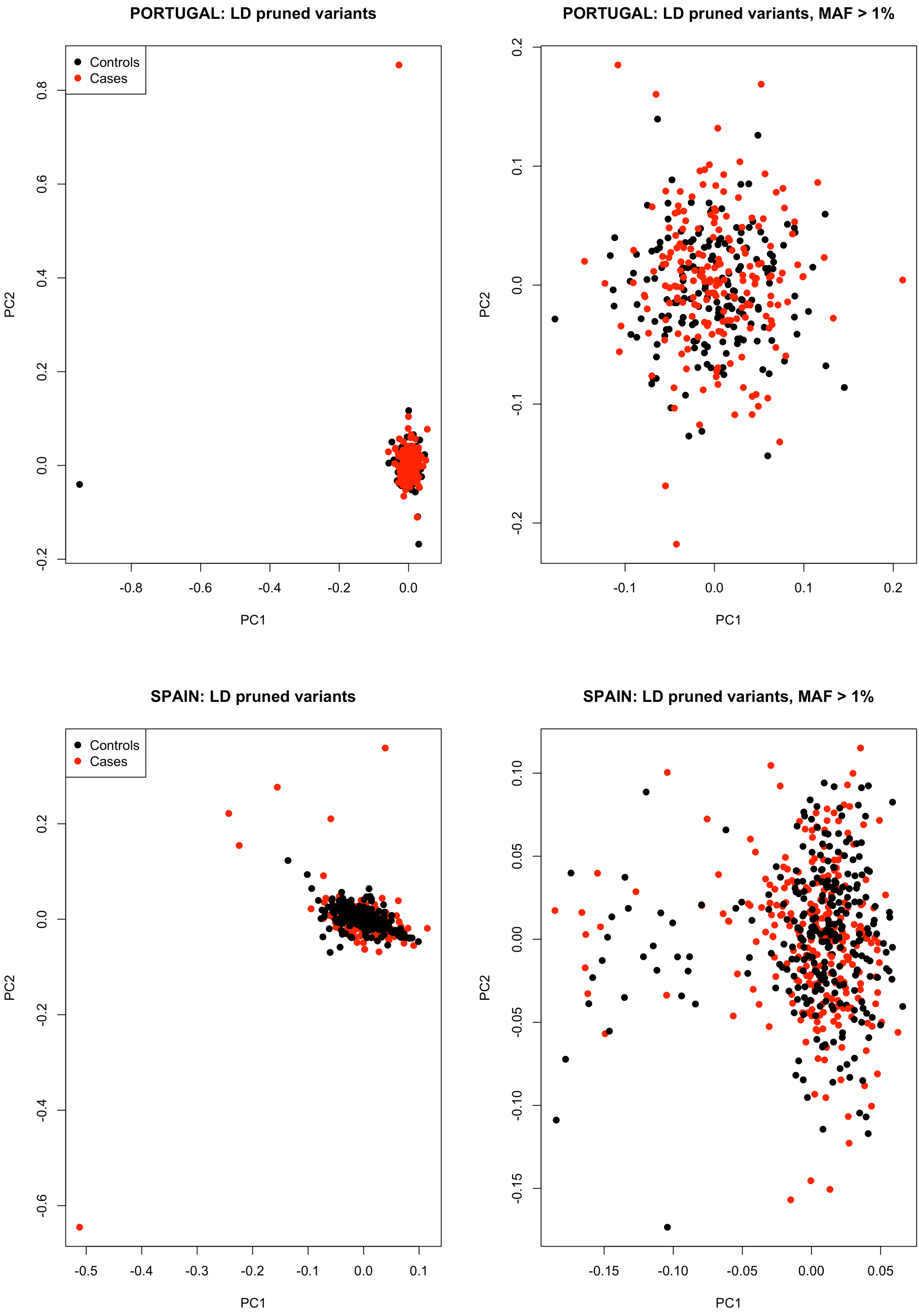


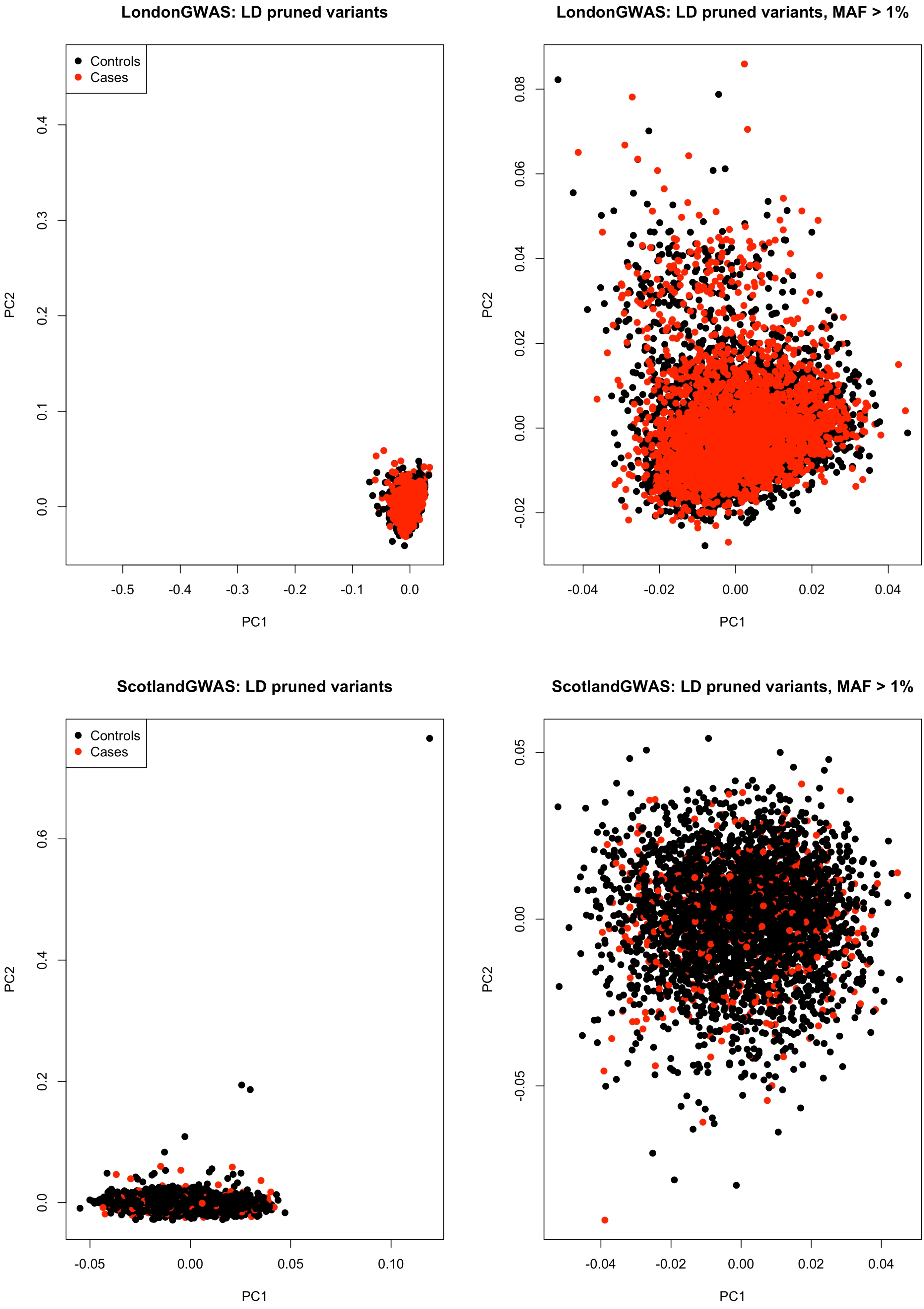
GERMANY: LD pruned variants

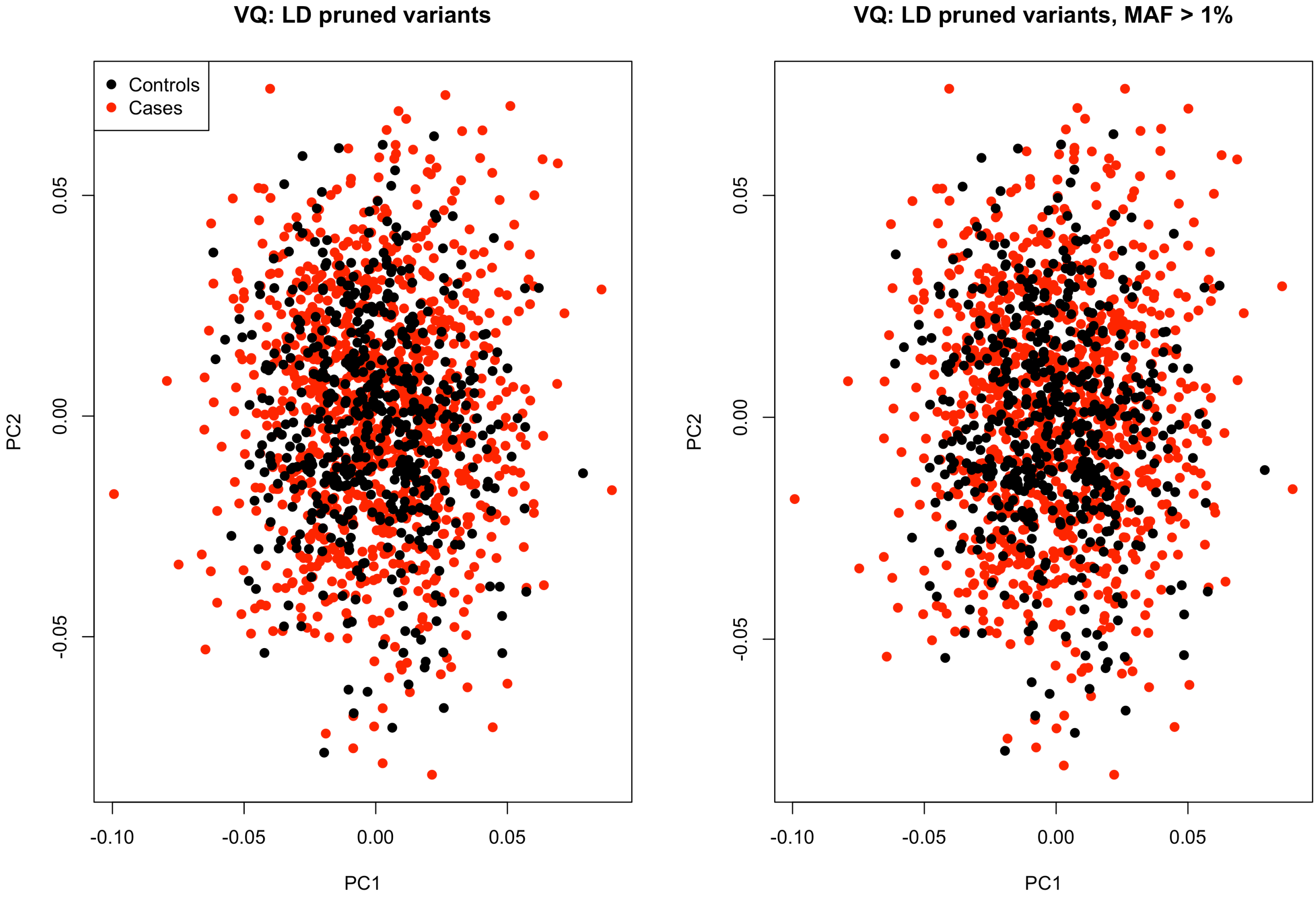
GERMANY: LD pruned variants, MAF > 1%

HOLLAND: LD pruned variants

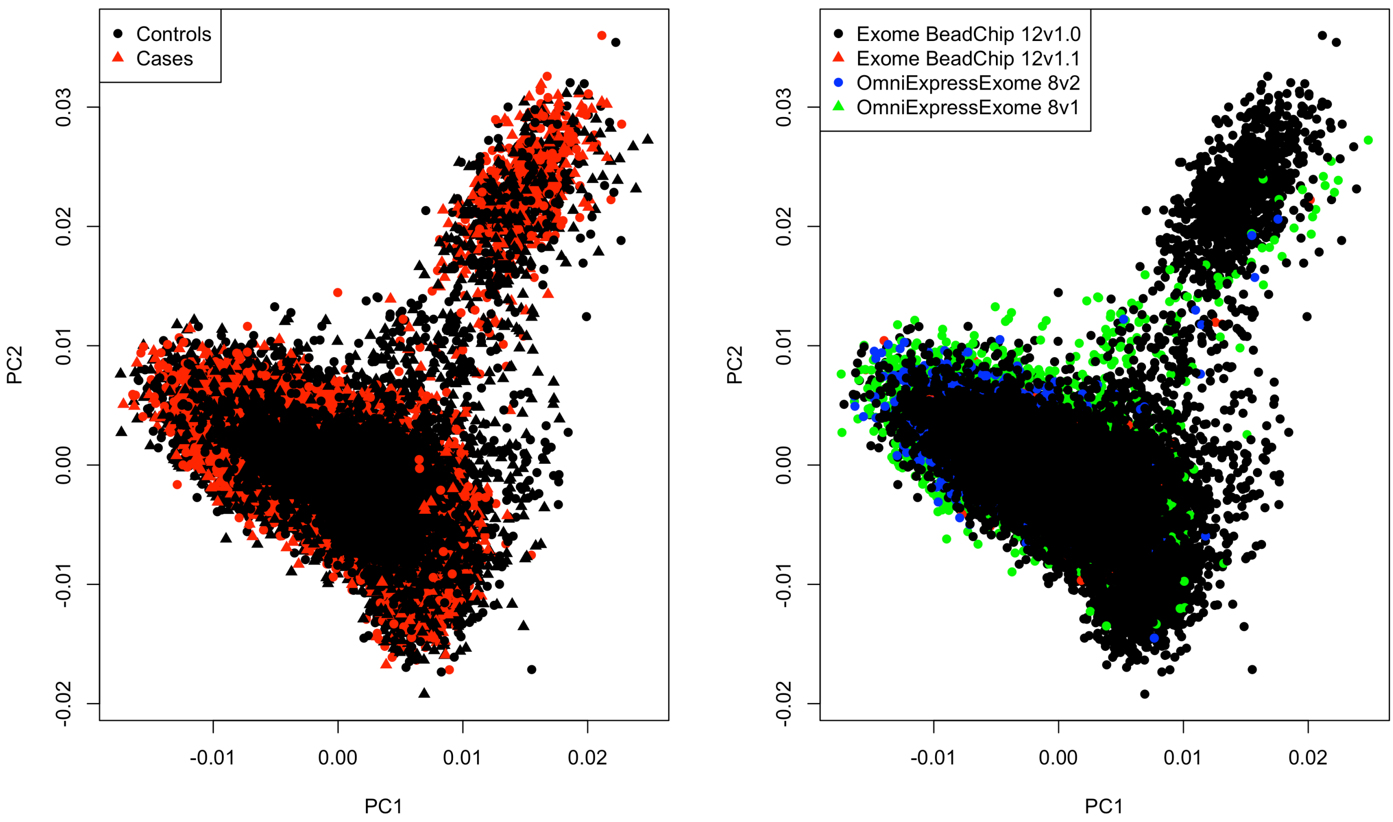
HOLLAND: LD pruned variants, MAF > 1%


PORTUGAL: LD pruned variants
Controls
Cases
PC2
0.8
0.6
0.4
0.2
0.0
-0.2
PC1
-0.8
-0.6
-0.4
-0.2
0.0
PORTUGAL: LD pruned variants, MAF > 1%
PC2
0.2
0.1
0.0
-0.1
-0.2
PC1
-0.1
0.0
0.1
0.2
SPAIN: LD pruned variants
Controls
Cases
PC2
0.2
0.0
-0.2
-0.4
-0.6
PC1
-0.5
-0.4
-0.3
-0.2
-0.1
0.0
0.1
SPAIN: LD pruned variants, MAF > 1%
PC2
0.10
0.05
0.00
-0.05
-0.10
-0.15
PC1
-0.15
-0.10
-0.05
0.00
0.05

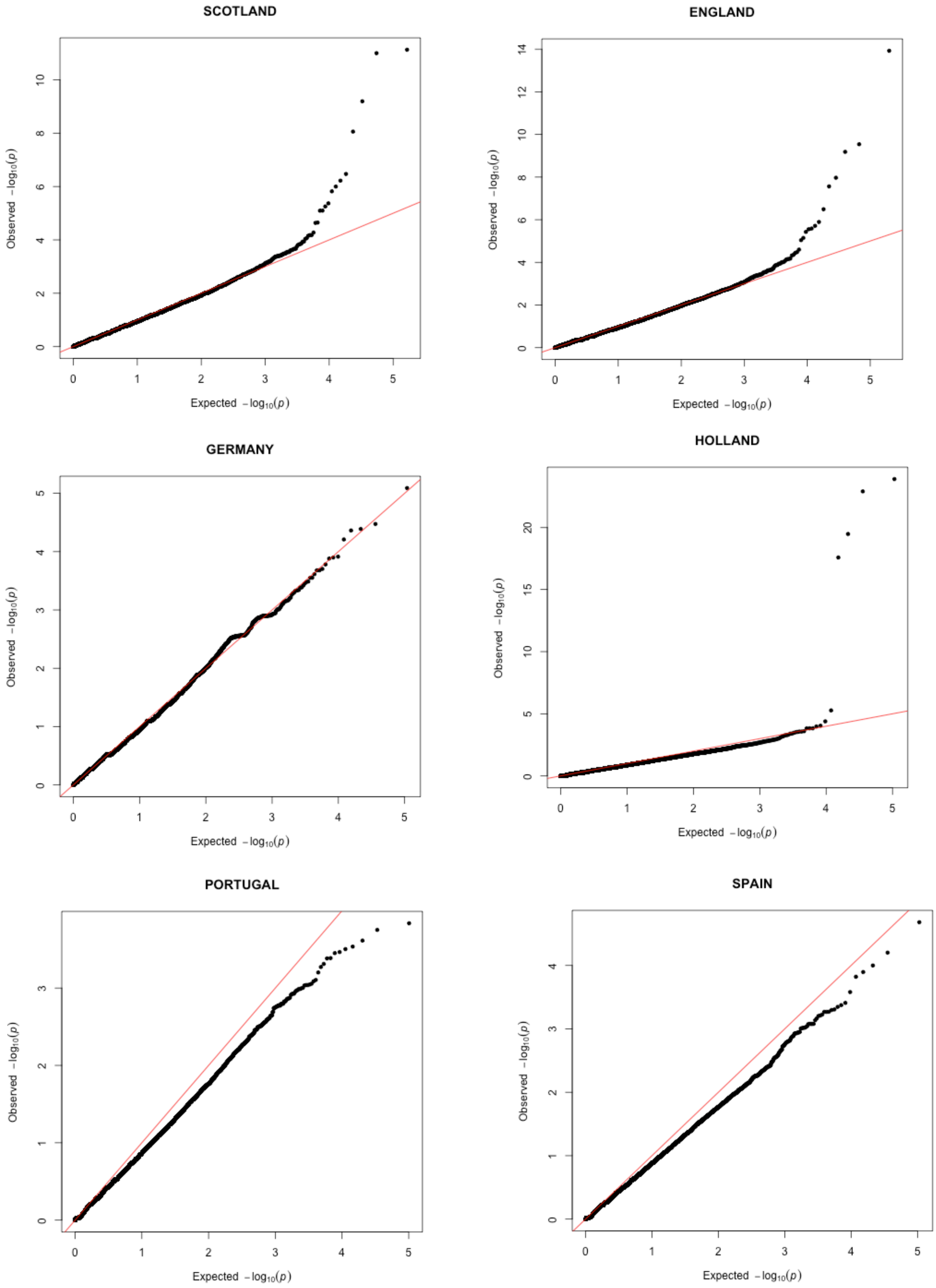

LondonGWAS: LD pruned variants
Controls
Cases
PC2
PC1
0.4
0.3
0.2
0.1
0.0
-0.5
-0.4
-0.3
-0.2
-0.1
0.0
LondonGWAS: LD pruned variants, MAF > 1%
PC2
PC1
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.02
0.00
0.02
0.04
ScotlandGWAS: LD pruned variants
Controls
Cases
PC2
PC1
0.6
0.4
0.2
0.0
-0.05
0.00
0.05
0.10
ScotlandGWAS: LD pruned variants, MAF > 1%
PC2
PC1
0.05
0.00
-0.05
-0.04
-0.02
0.00
0.02
0.04



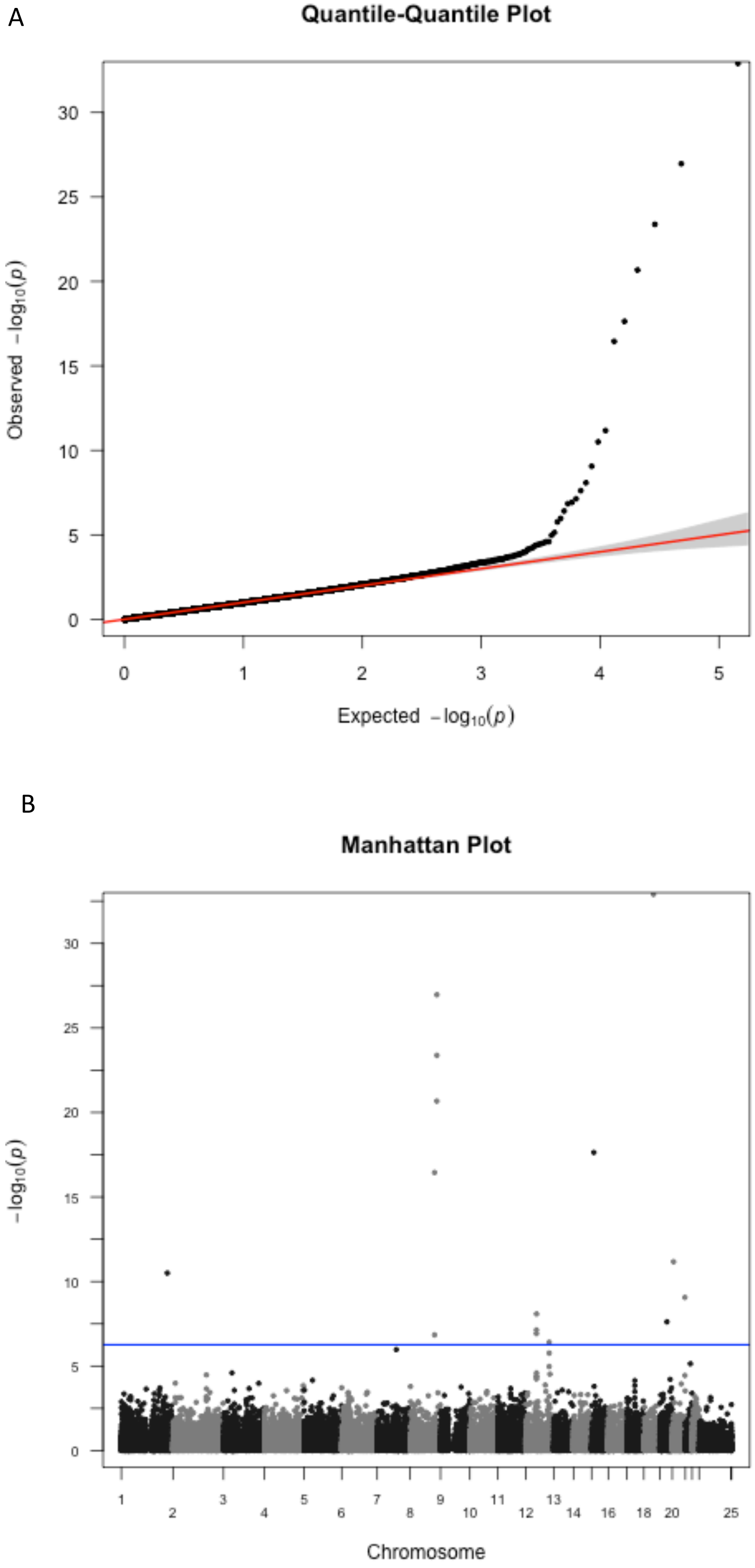
Supplementary Figure 4: Identification of non random clustering between cases and controls in different studies using principal component analysis. . LD prunning prior analysis was done in PLINK to exclude highly correlated variants (Parameter used for pruning : --indep-pairwise 100 5 0.1). (A) All variants; (B) All variants with allele frequency above 1%.



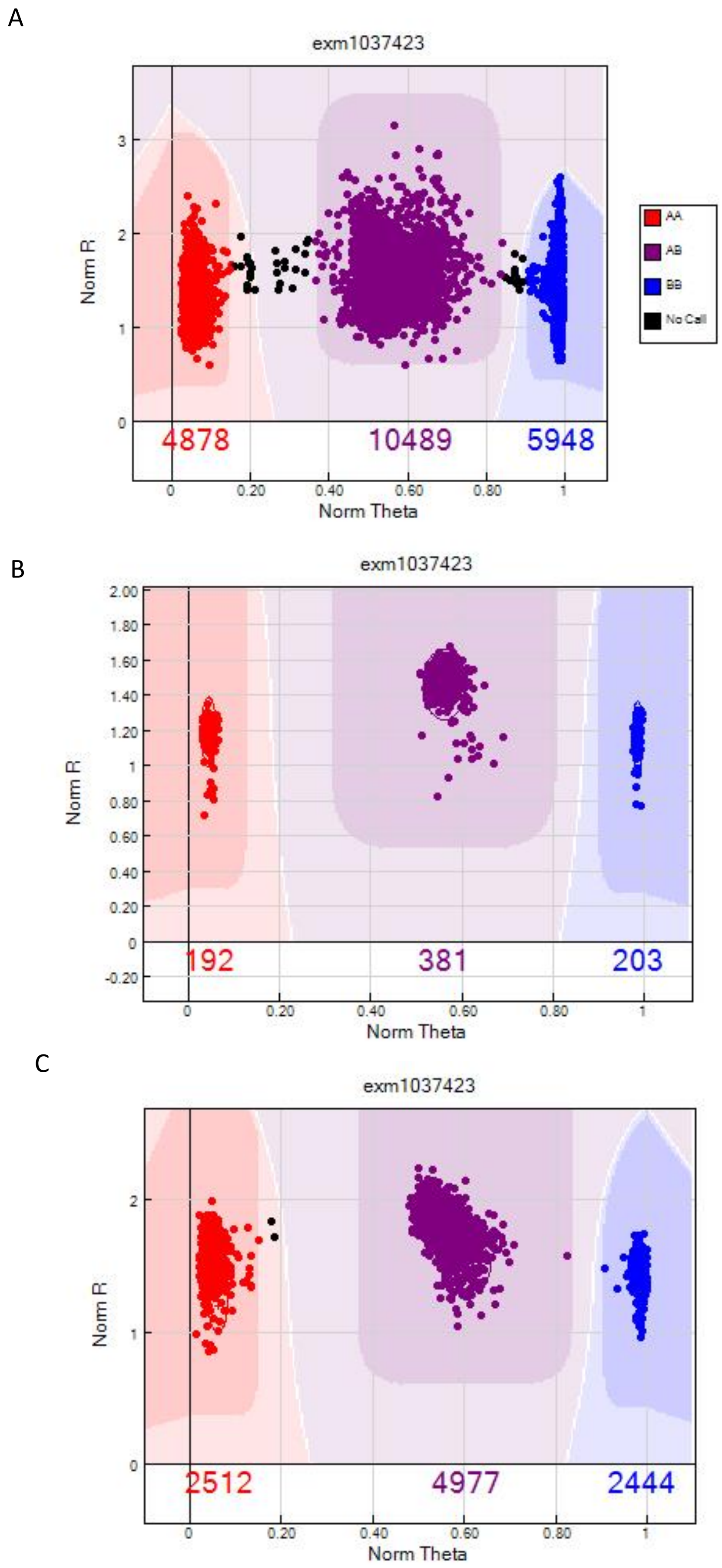
Supplementary Figure 5: Identification of non random clustering between all cases and controls (A) and between samples genotyped on different arrays using principal component analysis. LD prunning on the final list of variants after all quality control procedures (MAF>0.001) was done in PLINK to exclude highly correlated variants (Parameter used for pruning : --indep-pairwise 100 5 0.1)



Supplementary Figure 6: Quantile-Quantile (Q-Q) plots of observed and expected p values in –log10 scale of association between SNP genotype and colorectal cancer risk in six European studies. (a) Scotland, genomic inflation factor lambda (λ) =0,96; (b) England, λ =0,96; (c) Germany, λ =0,96; (d) Holland, λ =0,88; (e) Portugal, λ =0,84 and (f) Spain, λ =0,85.

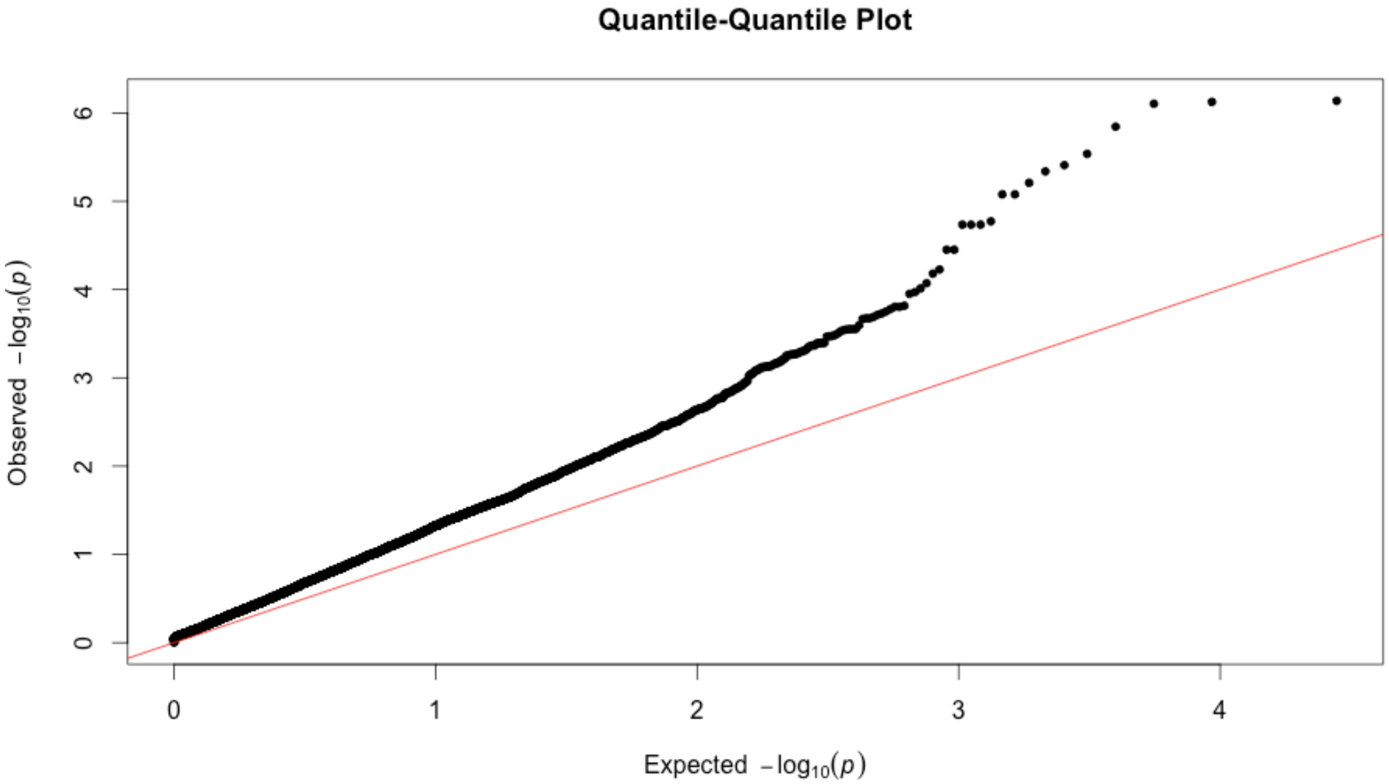


Supplementary Figure 7: QQ plot of observed and expected p-values in –log10 scale (A) and Manhattan (B) plots of association between 72,162 non-monomorphic variants and colorectal cancer risk in a meta-analysis comprising of 12638 cases and 29048 controls of European origin.

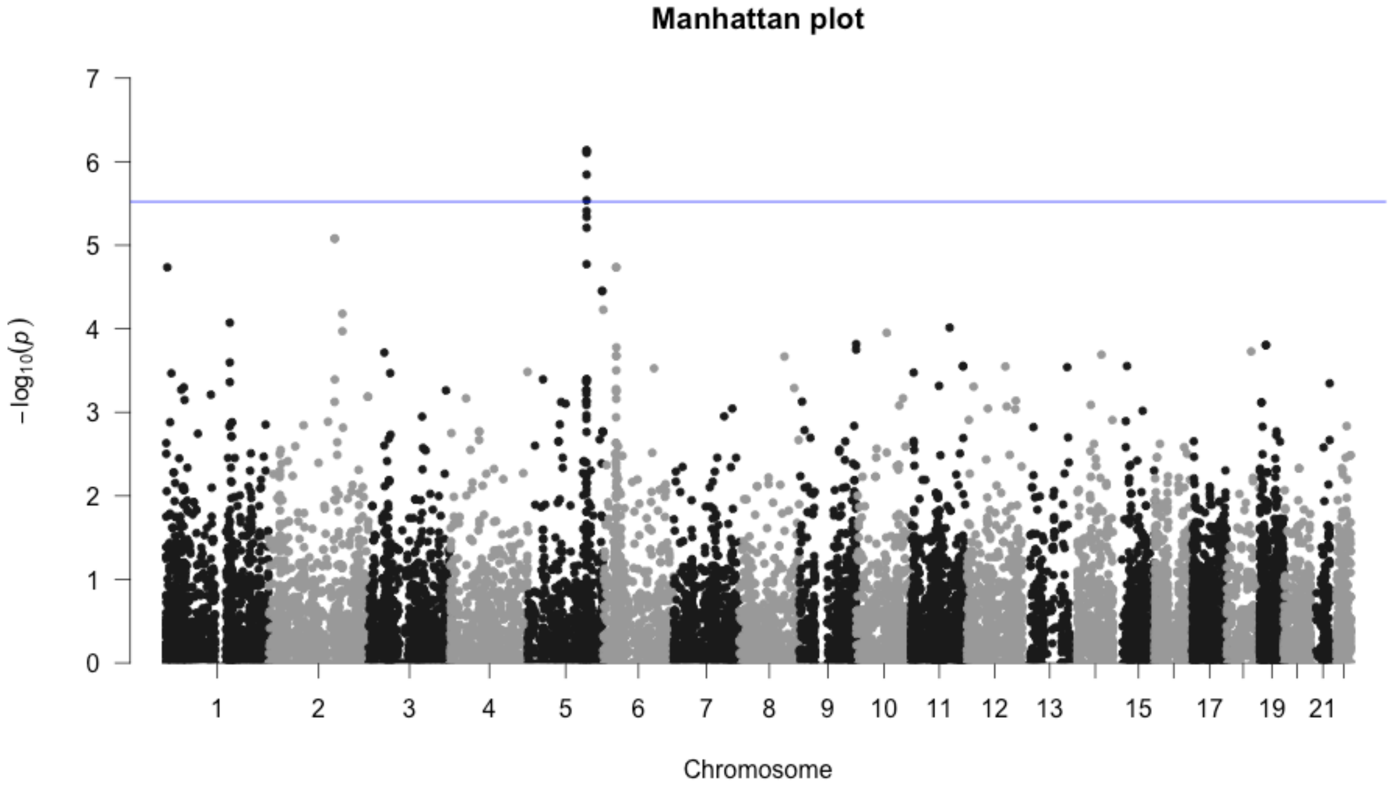


Supplementary Figure 8: Cluster plots for rs3184504 (*SH2B3*, 12q24) variant in different arrays.
(A) Infinium Human Exome BeadChip 12v1.0, (B) Infinium Human Exome BeadChip 12v1.1 , (C) OmniExpressExome BeadChip 8v1.1

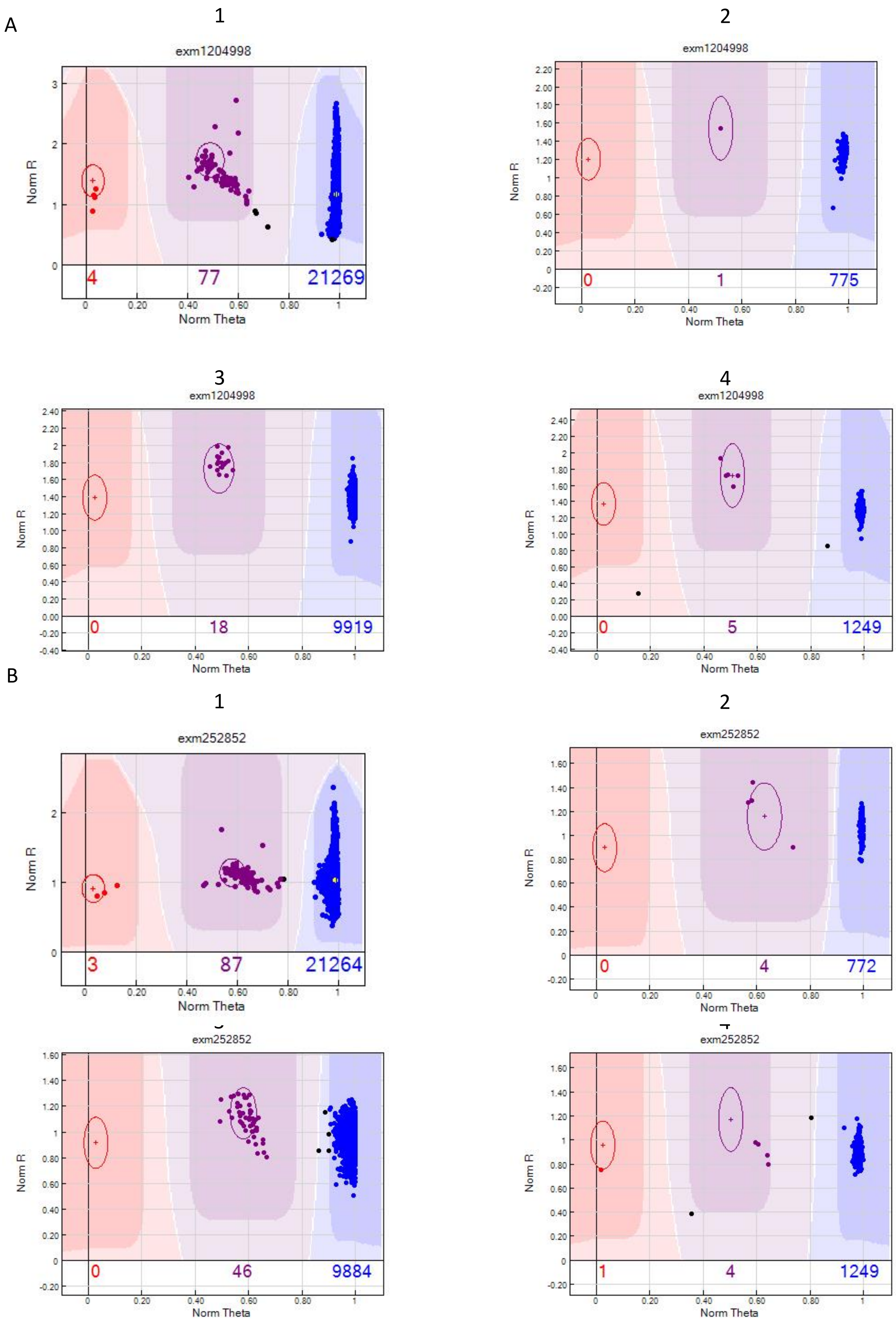
A



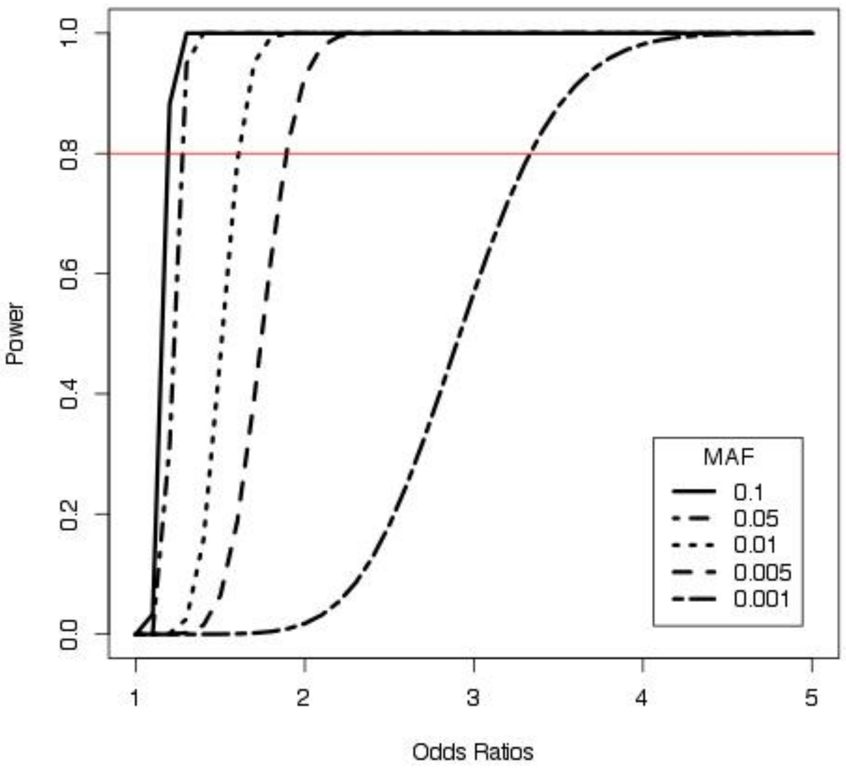
B



Supplementary Figure 9: QQ plot of observed and expected P-values in – $\log_{10}$ scale (A) and Manhattan (B) plots of association between 16,585 genes and colorectal cancer risk in a gene-based meta-analysis comprising of 12638 cases and 29045 controls of European origin.



Supplementary Figure 10: Cluster plots for rs150766139 (p.Gln90*,*NTHL1*, 16p13.3,exm1204998) and rs61756360 (p.Thr75Ile,PMS1, 2q32.2,exm252852) variants in different arrays.
(1) Infinium Human Exome BeadChip 12v1.0, (2) Infinium Human Exome BeadChip 12v1.1 , (3) OmniExpressExome BeadChip 8v1.1, (4) OmniExpressExome BeadChip 8v1.2.



Supplementary Figure 11: Power to detect CRC susceptibility variants over different effect size (OR) and for various minor allele frequencies (MAF).

Supplementary Table 1. Distribution of cases and controls by study.

Studies	Cases	Controls	N of variants after QC	N of nonmonomorphic variants contributing to meta-analysis
Scotland Exome	3418	9350	192460	109465
England	3584	10590	192460	118938
Germany	247	1053	192460	68005
Holland	397	376	192120	56527
Spain	259	273	192030	57351
Portugal	195	178	192342	53132
Overall Exome Array	**8100**	**21820**	**192460**	
UK1+UK2	3033	3690	9853	9749
Scotland	556	2997	8789	8626
VQ/58	949	538	7545	7545
Overal Replication	**4538**	**7225**		
Overall	**12638**	**29045**		72,162

Supplementary Table 2 . Sample and probe exclusion by study.

	England	**Scotland**	**Germany**	**Holland**	**Spain**	**Portugal**
QC on samples						
Pre-QC (cases/controls)	4 558/11 249	3 616/10 312	284/1 100	480/480	300/300	200/200
Individual QC by study	1,191					
LeedsYork	30					
OXBB	0					
ENGLAND_WALES	38					
	3 661/10 888					
Missing rate per person (>0.01)	9	151	45	115	22	2
Inbreeding, sample contamination (mean heterozygosity rate ± 3sd/6sd)	29	19	0	0	0	0
Population outliers (ACTA and STRUCTURE outliers)	77	105	34	59	32	14
Diagnosed with cancer (for population-based controls)		184	0	0	0	0
Sex discrepencies	191	47	0	0	0	0
Other (apendix, adenoma cases, sample swap, the same ID as case and as a control)		21	0	0	12	0
Between study duplicates, first degree relatives	69	617	5	14	2	11
Genotyping duplicates		16				
Post QC (cases/controls)	3 584/10 590	3 418/9 350	247/1 053	397/376	259/273	195/178
QC on probes						
Strand problem		14				
deviation from HWE (p<=0.001 in controls)	914	504	910	1,246	165	124
Missing rate	8,969	28,571	6,052	7,335	4,166	2,959
Missing by case-control status	11,318	19,538	3,858	511	626	4
Differences in call rate and frequency between different version of arrays	33,922	6,783	44,826	46,841	50,719	52,455
Monomorphic variants (MAF=0)	73,522	91,634	124,455	135,593	134,679	139,210
Final list of non-monomoprhic variants	118,938	109,465	68,005	56,527	57,351	53,132

Supplementary Table 3. Exclusion of between study duplicates for GWAS studies.

	UK Phase 1 and 2	Scotland Phase 1 and 2 and Phase 3*	VQ
QC on samples			
GWAS QC (ca/co) #	3 549/3 698	3 158/3 073	1 794/2 686
Other (known dominant polyposis syndromes, HNPCC/ Lynch syndrome, adenoma cases)	294	20	0
Additional between studies duplicates and relatives †	230	2658	2993
Post-QC (ca/co)	3 033/3 690	556/2 997	949/538
Non monomorphic variants overlapping with Illumina Exome Array	9749	8626	7545

# Details of QC are presented elsewhere (Dunlop et al., 2012).

* Quality Control for Scotland 3 was done following strandard protocol. 9 individuals overlapping with Scotland 1 and 15 adenoma and non cancer cases were excluded from the analysis.

†Duplicated samples were preferentially removed from these datasets over datasets with available exome-wide data .

Supplementary Table 4. Top results (p value <0.0001) for the meta-analysis

								Risk Allele Frequency				England				Scotland			Holland			Spain			Germany			Portugal			VQ			London GWAS			Scotland GWAS		
SNP	rsid	CHR	BP	PPgene	A1	A2	N	Cases	Controls	OR.fixed	P.fixed	I2	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls	OR.fixed	Cases	Controls
exm-rs4939827	rs4939827	18	46453463	*SMAD7*	A	G	9	0.57	0.52	1.21	1.3E-33	0	1.24	1168/1757/658	2859/5257/2472	1.22	1066/1746/606	2520/4665/2157	1.12	110/206/80	99/185/92	1.26	99/115/45	78/143/52	1.23	80/116/51	267/533/253	1.07	61/92/42	53/83/42	1.16	299/467/182	143/280/115	1.19	968/1494/571	1001/1847/842	1.15	171/279/106	829/1474/694
exm-rs6983267	rs6983267	8	128413305		C	A	9	0.56	0.52	1.19	1.1E-27	0	1.19	1127/1798/659	2882/5300/2408	1.15	1033/1716/668	2520/4675/2155	1.13	121/208/68	114/176/86	1.13	91/124/44	90/123/58	1.28	76/123/47	261/528/264	1.07	71/86/38	57/88/33	1.13	272/481/194	141/268/129	1.24	956/1510/567	975/1813/900	1.26	174/292/90	821/1461/715
exm-rs7014346	rs7014346	8	128424792		A	G	9	0.41	0.37	1.17	4.2E-24	0	1.17	611/1738/1234	1519/4924/4147	1.16	572/1665/1180	1311/4409/3630	1.09	74/189/134	63/178/135	1.21	48/117/94	42/114/117	1.20	40/123/84	144/487/422	1.19	32/96/67	26/79/73	1.24	144/471/333	67/243/228	1.20	528/1441/1064	518/1674/1497	1.18	84/291/181	429/1385/1183
exm-rs10505477	rs10505477	8	128407443		A	G	9	0.55	0.51	1.17	2.1E-21	0	1.19	1087/1808/689	2777/5322/2491	1.14	1006/1705/706	2456/4668/2225	1.08	116/202/79	109/178/89	1.15	87/124/48	85/123/64	1.25	71/125/51	245/532/276	1.10	66/90/39	53/88/37	0.87	05/04/2006	137/267/134	1.21	758/1244/492	722/1380/689	1.31	58/109/29	530/992/500
exm-rs4779584	rs4779584	15	32994756		A	G	9	0.21	0.19	1.19	2.3E-18	0	1.15	156/1220/2208	386/3277/6926	1.16	165/1094/2159	285/2887/6178	1.41	19/130/247	7/107/262	1.47	12/84/163	6/71/196	1.20	16/84/147	37/356/660	1.54	7/68/120	4/45/129	1.15	51/293/605	15/170/353	1.22	163/998/1871	126/1117/2446	1.27	18/123/219	37/279/659
exm-rs16892766	rs16892766	8	117630683		C	A	9	0.10	0.08	1.26	3.6E-17	0	1.25	37/629/2918	64/1571/8955	1.25	29/635/2754	63/1426/7861	1.05	4/69/324	3/64/309	1.17	0/35/224	2/28/243	1.33	6/41/200	1/174/878	1.44	3/39/153	3/23/152	0.94	1/0/14	3/70/465	1.36	24/555/2454	19/520/3151	1.17	5/98/453	19/467/2511
exm-rs961253	rs961253	20	6404281		A	C	9	0.39	0.36	1.12	6.8E-12	0	1.12	526/1715/1342	1379/4865/4346	1.10	515/1622/1281	1269/4307/3774	1.08	77/191/129	63/187/126	1.14	32/122/105	28/124/121	1.24	50/95/102	127/467/459	1.16	26/91/78	22/74/82	0.96	0/11/4	77/251/210	1.10	460/1399/1174	477/1698/1515	1.25	93/266/197	386/1344/1267
exm-rs6687758	rs6687758	1	222164948		G	A	9	0.22	0.20	1.14	3.2E-11	0	1.17	177/1224/2181	425/3249/6915	1.11	157/1153/2107	379/2927/6027	1.19	17/141/239	11/123/242	1.23	14/88/156	9/86/178	1.20	9/92/146	38/331/684	1.08	6/66/123	5/57/116	0.97	48/306/592	24/186/326	1.11	120/1040/1872	129/1180/2381	1.21	30/192/334	110/946/1941
exm-rs4925386	rs4925386	20	60921044	*LAMA5*	G	A	9	0.71	0.68	1.11	8.7E-10	0	1.09	1753/1510/320	4965/4511/1113	1.17	1741/1403/273	4352/4065/932	1.15	206/159/32	182/155/39	1.12	126/111/22	124/122/27	0.96	119/100/28	491/475/87	1.10	99/80/16	82/83/13	1.09	469/392/88	253/228/57	1.10	1505/1285/243	1746/1590/354	1.10	97/82/17	942/885/195
exm1002721	rs1129406	12	51203371	*ATF1*	A	G	6	0.43	0.40	1.11	8.3E-09	14	1.14	666/1762/1156	1662/5163/3765	1.10	609/1726/1083	1566/4483/3300	1.03	67/183/147	63/168/145	1.37	50/145/64	42/135/96	0.98	42/107/98	180/466/407	1.04	39/96/60	38/79/61	NA	NA	NA	NA	NA	NA	NA	NA	NA
exm-rs10411210	rs10411210	19	33532300	*RHPN2*	G	A	9	0.92	0.91	1.18	2.4E-08	23.9	1.12	3041/522/20	8820/1694/76	1.20	2933/469/16	7799/1484/66	1.02	347/46/4	328/44/4	0.82	196/61/2	218/52/3	1.32	217/28/2	885/159/9	1.80	162/30/3	126/49/3	0.86	12/03/2000	447/88/3	1.20	2563/448/21	3014/647/29	1.38	479/73/3	2451/522/24
exm1002434	rs12303082	12	50754563	*FAM186A*	A	C	9	0.37	0.35	1.09	7.4E-08	9.15	1.11	490/1671/1423	1249/4850/4491	1.06	458/1654/1306	1253/4253/3843	1.03	41/173/183	42/152/182	1.33	40/138/81	34/127/112	0.94	25/105/117	128/437/488	0.96	25/102/68	27/88/63	1.17	102/495/352	53/255/230	1.13	423/1425/1184	421/1711/1558	1.00	22/98/76	268/929/825
exm1002264	rs6580742	12	50727811	*FAM186A*	A	G	9	0.20	0.19	1.11	1.2E-07	0	1.13	147/1153/2284	357/3151/7082	1.09	163/1150/2105	383/2996/5971	0.89	7/106/284	15/96/265	1.23	9/78/172	8/69/196	0.91	7/61/179	35/277/741	1.12	7/56/132	5/48/125	1.22	34/310/605	11/161/366	1.12	132/985/1916	128/1133/2429	1.09	25/183/348	112/947/1938
exm716877	rs16888728	8	117783975	*UTP23*	A	G	8	0.11	0.10	1.15	1.4E-07	0	1.16	41/705/2838	101/1831/8658	1.13	43/665/2710	88/1664/7597	0.84	4/79/314	4/88/284	1.12	1/37/221	2/33/238	1.30	8/44/195	4/195/854	1.38	7/45/143	2/36/140	NA	NA	NA	1.20	29/479/1986	20/470/2302	1.15	3/36/157	12/359/1651
exm1037423	rs3184504	12	111884608	*SH2B3*	G	A	9	0.53	0.51	1.08	3.9E-07	0	1.07	1023/1780/781	2816/5297/2476	1.09	932/1689/797	2328/4646/2374	1.10	137/178/82	116/177/83	1.12	75/140/44	78/134/60	1.18	64/130/53	250/512/291	1.08	60/91/44	48/90/40	1.19	270/468/211	123/279/136	1.07	876/1532/620	1012/1847/825	0.99	133/291/130	769/1490/737
exm-rs2282978	rs2282978	7	92264410	*CDK6*	G	A	9	0.34	0.32	1.08	1.1E-06	15.3	1.04	415/1569/1600	1124/4669/4795	1.12	366/1540/1512	894/3986/4469	0.96	52/170/175	44/179/153	1.13	50/125/84	43/135/95	0.95	29/101/116	107/492/454	1.23	42/90/63	25/91/62	1.15	116/407/425	54/220/264	1.09	362/1341/1329	372/1623/1695	1.19	72/250/234	317/1254/1426
exm-rs653178	rs653178	12	112007756	*ATXN2*	A	G	8	0.53	0.51	1.09	1.7E-06	0	1.07	1016/1786/782	2803/5307/2480	1.09	925/1692/801	2312/4650/2387	1.11	136/180/81	115/177/84	1.14	75/140/44	77/135/61	1.17	62/132/53	249/511/293	1.06	60/91/44	48/91/39	1.20	270/469/210	122/279/136	1.01	134/281/124	230/452/216	NA	NA	NA
exm-rs1209950	rs1209950	21	40173528		A	G	6	0.43	0.41	1.09	7.3E-06	0	1.07	661/1711/1212	1732/5175/3682	1.10	629/1671/1118	1554/4472/3322	1.30	83/179/135	49/179/147	1.08	57/126/76	56/130/87	1.06	39/119/89	154/502/397	1.12	33/101/61	27/89/62	NA	NA	NA	NA	NA	NA	NA	NA	NA
exm-rs10774625	rs10774625	12	111910219	*ATXN2*	G	A	6	0.52	0.49	1.09	1.1E-05	0	1.07	967/1786/831	2664/5300/2626	1.09	869/1697/852	2184/4642/2524	1.15	135/180/82	111/176/89	1.09	73/139/47	77/134/61	1.20	63/130/54	243/510/300	1.09	60/90/45	46/92/40	NA	NA	NA	NA	NA	NA	NA	NA	NA
exm2265440	rs6599132	3	41039907		G	A	9	0.57	0.55	1.08	2.5E-05	0	1.06	1152/1798/634	3256/5300/2033	1.11	1115/1670/633	2735/4708/1907	1.11	113/203/80	102/184/90	1.18	97/126/36	94/127/52	1.10	78/123/46	307/529/217	0.90	68/87/40	62/89/27	0.98	296/471/182	180/247/111	1.02	166/272/101	278/440/180	1.06	111/172/77	290/458/227
exm-rs11169552	rs11169552	12	51155663		G	A	9	0.75	0.73	1.08	2.6E-05	0	1.08	1985/1375/224	5670/4117/801	1.10	1910/1309/199	5000/3687/663	1.04	229/145/23	217/132/27	0.83	149/95/15	172/88/13	0.94	132/102/13	598/388/67	1.25	123/63/9	101/66/11	1.18	553/348/48	287/218/33	1.06	1698/1115/220	1974/1452/263	1.04	290/231/33	1574/1199/224
exm-rs7315438	rs7315438	12	115891403		A	G	9	0.59	0.57	1.08	3.0E-05	14.3	1.06	1280/1697/604	3585/5093/1911	1.09	1189/1631/597	2971/4635/1741	1.05	159/176/62	147/163/65	0.96	68/127/64	70/143/60	1.22	96/118/32	347/538/168	0.75	45/92/58	49/94/35	1.10	339/466/144	174/277/87	1.13	202/258/79	300/451/147	1.11	122/187/51	326/468/181
exm235708	rs78446341	2	160690656	*LY75*	A	G	6	0.03	0.02	1.27	3.3E-05	0	1.24	4/191/3389	7/461/10122	1.30	1/226/3191	4/479/8867	1.30	0/15/382	0/11/365	1.69	0/11/248	0/7/266	1.03	0/7/240	0/29/1024	1.10	0/12/183	0/10/168	NA	NA	NA	NA	NA	NA	NA	NA	NA
exm1556471	rs2236200	20	60986019	*C20orf151*	A	C	9	0.76	0.74	1.08	3.6E-05	0	1.09	2056/1320/208	5813/4080/696	1.10	1986/1246/185	5220/3502/624	1.13	232/144/20	208/145/23	1.07	148/93/18	142/118/12	1.11	141/101/5	603/389/61	1.12	128/57/10	108/63/7	1.05	566/332/50	322/178/38	1.04	1686/1164/182	2002/1465/223	1.00	109/75/12	1122/777/123
exm1002260	rs6580741	12	50727706	*FAM186A*	G	C	6	0.37	0.35	1.08	3.9E-05	19.9	1.11	490/1675/1419	1252/4850/4485	1.07	459/1651/1307	1250/4229/3842	1.04	42/172/183	42/152/182	1.35	39/140/80	33/128/112	0.94	25/105/117	128/436/489	0.96	25/100/70	27/86/65	NA	NA	NA	NA	NA	NA	NA	NA	NA
exm1002762	rs861204	12	51237816	*TMPRSS12*	G	A	9	0.67	0.66	1.07	4.2E-05	5.75	1.08	1623/1572/388	4547/4801/1242	1.06	1545/1485/388	4028/4206/1112	0.97	168/175/54	154/181/41	1.45	120/117/22	103/123/46	1.14	110/109/28	431/477/145	0.89	85/83/27	79/82/17	1.01	402/442/104	222/260/56	1.07	1432/1262/334	1627/1649/407	1.07	256/242/57	1314/1348/334
exm1002276	rs7296291	12	50744119	*FAM186A*	G	A	6	0.37	0.35	1.08	5.8E-05	18	1.11	490/1671/1423	1249/4850/4491	1.06	457/1654/1306	1250/4254/3843	1.03	42/172/183	42/153/181	1.33	40/138/81	34/127/112	0.94	25/105/117	128/437/488	0.96	25/102/68	27/88/63	NA	NA	NA	NA	NA	NA	NA	NA	NA
exm1488109	rs2307019	19	49244220	*IZUMO1*	G	A	9	0.59	0.58	1.07	6.1E-05	2.3	1.07	1229/1719/635	3410/5168/2010	1.07	1315/1612/489	3378/4537/1432	1.33	126/195/76	90/191/95	1.06	81/127/51	83/130/60	1.16	77/122/48	284/532/237	1.04	56/93/46	55/73/50	0.94	312/460/177	194/244/100	1.10	189/259/91	286/450/162	1.04	136/176/48	372/450/153
exm-rs2548145	rs2548145	5	40134777		G	A	8	0.54	0.52	1.07	6.9E-05	1.98	1.08	1053/1763/768	2859/5288/2442	1.10	998/1735/685	2557/4641/2151	0.88	92/194/111	89/204/83	1.04	80/127/52	87/123/63	1.06	62/133/52	272/520/261	1.08	66/96/33	54/94/30	1.02	273/456/220	144/274/120	0.97	146/278/115	251/463/184	NA	NA	NA
exm-rs11869286	rs11869286	17	37813856	*STARD3*	C	G	6	0.34	0.32	1.08	7.3E-05	0	1.08	423/1652/1509	1160/4699/4730	1.08	387/1500/1530	929/4046/4358	1.13	50/186/161	44/162/170	1.22	37/134/88	34/127/112	1.05	25/108/114	111/430/512	1.02	29/94/72	25/87/66	NA	NA	NA	NA	NA	NA	NA	NA	NA

Supplementary Table 5. Results of conditional analysis for 12q24.12 locus.

								Results of meta-analysis			Conditional to rs3184504		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**
exm1037167	C	rs200420920	12	111652019	CUX2	missense	0.9995	2	1.1103	0.8273	2	1.1422	0.7817
exm1037169	A	rs199531850	12	111652040	CUX2	missense	0.0003	2	1.7067	0.3008	2	1.7488	0.2794
exm1037224	G	rs201856438	12	111744903	CUX2	missense	0.0002	2	1.5745	0.5784	2	1.492	0.6242
exm1037295	G	rs201719553	12	111776225	CUX2	missense	0.0002	2	1.1957	0.8288	2	1.2584	0.7812
exm1037299	A	rs200121526	12	111779619	CUX2	missense	0.0002	2	1.6207	0.4773	2	1.6255	0.4748
exm1037318	A	rs61745424	12	111785515	CUX2	missense	0.0240	6	1.1162	0.06097	6	1.0841	0.1722
exm1037367	A	rs201849141	12	111800849	FAM109A	missense	0.0023	4	1.2243	0.2721	4	1.1781	0.3745
exm1037423	G	rs3184504	12	111884608	SH2B3	missense	0.5072	9	1.0822	3.877E-07	#N/A	#N/A	#N/A
exm1037447	G	rs72650673	12	111885310	SH2B3	missense	0.9970	2	1.1421	0.471	2	1.1878	0.3511
exm1037482	A	rs72650662	12	111886074	SH2B3	missense	0.0003	2	0.9477	0.926	2	0.9125	0.8741
exm1037483	A	rs148791142	12	111886075	SH2B3	missense	0.0003	2	1.0846	0.8781	2	1.0283	0.9579
exm1037484	G	rs199803113	12	111886081	SH2B3	missense	0.0003	2	2.4032	0.03785	2	2.3719	0.04087
exm1037527	G	rs140262591	12	111908545	ATXN2	coding-synon	0.0057	5	1.0563	0.6539	5	1.0189	0.8786
exm-rs10774625	G	rs10774625	12	111910219	ATXN2	intron	0.4930	6	1.0851	1.06E-05	6	0.9971	0.9698
exm1037532	A	rs142462470	12	111923594	ATXN2	missense	0.0004	4	1.1942	0.6806	4	1.1424	0.7576
exm1037574	G	rs117851901	12	111956226	ATXN2	missense	0.0034	2	1.0263	0.8719	2	1.0686	0.6812
exm1037605	G	rs7969300	12	111993712	ATXN2	missense	0.9977	7	1.3863	0.1142	6	1.4486	0.07365
exm-rs653178	A	rs653178	12	112007756	ATXN2	intron	0.5058	8	1.0878	1.71E-06	8	0.9702	0.8762
exm-rs11065987	A	rs11065987	12	112072424			0.5747	9	1.0631	6.30E-04	9	0.9816	0.5983
exm1037707	A	rs148204415	12	112130611	ACAD10	missense	0.0012	2	1.7007	0.02406	2	1.6312	0.03792
exm1037760	G	rs200607092	12	112165819	ACAD10	missense	0.0011	2	1.2811	0.3422	2	1.2225	0.4416
exm1037802	A	rs138790472	12	112182585	ACAD10	missense	0.9993	3	1.2202	0.6413	3	1.2863	0.556
exm1037831	G	rs150349412	12	112184086	ACAD10	missense	0.9983	4	1.1962	0.4717	4	1.2559	0.3608
exm1037842	T	rs141918583	12	112185166	ACAD10	missense	0.0004	2	1.5619	0.2391	2	1.6538	0.1845
exm1037851	G	rs34245489	12	112186274	ACAD10	missense	0.9526	6	1.002	0.9641	6	0.973	0.5397
exm2259959	G	rs2238151	12	112211833	ALDH2	intron	0.3202	6	1.0177	0.3764	6	0.9688	0.1578
exm1037914	G	rs147086207	12	112221070	ALDH2	missense	0.0010	2	1.0448	0.8851	2	0.9991	0.9977

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 6. Results of conditional analysis for 8q23.3-8q24.11 locus.

								Results of meta-analysis			Conditional to rs16888728			Conditional to rs16892766		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N**	**OR.fixed**	**P.fixed**	**N**	**OR.fixed**	**P.fixed**
exm-rs799889	C	rs799889	8	117250895			0.18	6	1.02	0.40	6	1.02	0.42	6	1.01	0.55
exm-rs4876662	A	rs4876662	8	117556270			0.19	6	1.00	0.92	6	1.00	0.96	6	0.99	0.67
exm-rs16892766	**C**	**rs16892766**	**8**	**117630683**			0.08	**9**	**1.26**	**3.57E-17**	**8**	**1.27**	**5.13E-10**	**#N/A**	**#N/A**	**#N/A**
exm716811	A	rs200534489	8	117658748	*EIF3H*	missense	0.0002	2	2.23	0.26	2	2.29	0.24	2	2.32	0.23
exm716877	A	rs16888728	8	117783975	*UTP23*	missense	0.10	8	1.15	1.43E-07	#N/A	#N/A	#N/A	8	0.99	0.83
exm716893	G	rs139935751	8	117859924	*RAD21*	missense	1.00	2	1.43	0.64	4	1.44	0.64	3	1.40	0.66
exm716897	A	rs143363239	8	117861258	*RAD21*	missense	0.00025	2	2.07	0.12	2	2.12	0.11	2	2.11	0.11
exm716913	C	rs144953114	8	117864305	*RAD21*	missense	0.0005	2	1.17	0.72	2	1.18	0.70	2	1.19	0.68
exm716958	G	rs16889042	8	117879001	*RAD21*	intron	1.00	4	1.04	0.83	5	1.15	0.48	4	1.04	0.86

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 7. Results of conditional analysis for 12q13.12 locus.

								Results of meta-analysis			Conditional to rs1129406			Conditional to rs12303082			Conditional to rs6580742		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**	**N.cond**	**OR.cond**	**P.cond**	**N.cond**	**OR.cond**	**P.cond**
exm1002126	A	rs146787766	12	50535840	LASS5	missense	0.00018	2	2.39	0.15	2	2.49	0.13	2	2.45	0.14	2	2.44	0.14
exm1002141	G	rs7302981	12	50537815	LASS5	missense	0.626	9	1.05	1.40E-03	6	0.99	0.82	9	1.01	0.62	9	1.02	0.16
exm1002146	A	rs143484198	12	50561023	LASS5	missense	0.007	6	1.09	0.43	6	1.13	0.25	6	1.12	0.29	6	1.11	0.34
exm1002199	A	rs142007630	12	50586275	LIMA1	missense	0.00023	2	1.45	0.50	2	1.55	0.43	2	1.52	0.45	2	1.50	0.46
exm1002256	C	rs12809349	12	50724444	FAM186A	missense	0.036	6	1.16	1.75E-03	6	1.09	0.07	6	1.11	0.04	6	1.08	0.15
exm1002260	G	rs6580741	12	50727706	FAM186A	missense	0.352	6	1.08	3.92E-05	6	0.96	0.26	5	1.41	0.27	6	1.05	0.06
exm1002264	A	rs6580742	12	50727811	FAM186A	missense	0.189	9	1.11	1.20E-07	6	1.03	0.26	9	1.06	0.04	#N/A	#N/A	#N/A
exm1002266	G	rs80201036	12	50727870	FAM186A	nonsense	0.990	6	1.28	0.01	6	1.22	0.04	6	1.24	0.03	6	1.25	0.02
exm1002276	G	rs7296291	12	50744119	FAM186A	missense	0.353	6	1.08	5.76E-05	6	0.96	0.21				6	1.05	0.08
exm1002287	C	rs183549613	12	50744680	FAM186A	missense	0.0003	2	2.17	0.13	2	2.18	0.13	2	1.99	0.18	2	2.21	0.12
exm1002397	G	rs201058635	12	50748127	FAM186A	missense	0.998	3	1.07	0.74	3	1.03	0.90	3	1.04	0.86	3	1.05	0.83
exm1002414	C	rs4435082	12	50749221	FAM186A	missense	0.0002	3	1.09	0.89	3	1.06	0.93	3	0.99	0.99	3	1.12	0.86
exm1002415	C	rs4625558	12	50749227	FAM186A	missense	1.000	2	1.22	0.82	2	1.27	0.78	2	1.25	0.80	2	1.17	0.86
exm1002419	C	rs74090114	12	50749554	FAM186A	missense	0.989	6	1.03	0.78	6	0.99	0.89	6	1.00	0.98	6	1.01	0.91
exm1002434	A	rs12303082	12	50754563	FAM186A	missense	0.353	9	1.09	7.36E-08	6	0.96	0.21	#N/A	#N/A	#N/A	9	1.06	0.01
exm1002436	C	rs201711271	12	50754577	FAM186A	missense	0.00023	2	1.15	0.84	2	1.25	0.75	2	1.21	0.79	2	1.20	0.80
exm1002440	C	rs184587740	12	50757020	FAM186A	missense	0.999	2	1.33	0.54	4	1.24	0.64	2	1.27	0.60	2	1.28	0.59
exm2271842	G	rs10735825	12	50768339	FAM186A	intron	0.055	6	1.06	0.15	6	1.02	0.58	6	1.02	0.58	6	1.08	0.05
exm1002449	C	rs146142861	12	50821551	LARP4	missense	0.976	6	1.12	0.06	6	1.10	0.14	6	1.09	0.17	6	1.10	0.13
exm1002524	A	rs201453176	12	50869569	LARP4	missense	0.00013	2	1.52	0.50	2	1.43	0.57	2	1.46	0.55	2	1.41	0.59
exm-rs1087604	G	rs10876041	12	50901882	DIP2B	intron	0.637	6	1.05	0.02	6	0.96	0.10	6	1.00	0.84	6	1.02	0.39
exm1002555	A	rs73093419	12	51068409	DIP2B	missense	0.014	5	1.02	0.80	5	1.08	0.38	5	1.05	0.53	5	1.04	0.60
exm1002585	A	rs74751916	12	51080364	DIP2B	missense	0.021	6	1.05	0.41	6	0.99	0.93	6	1.01	0.91	6	1.08	0.24
exm1002587	C	rs148830732	12	51080389	DIP2B	missense	0.999	2	0.97	0.92	3	0.93	0.83	2	0.95	0.87	2	0.95	0.88
exm1002627	A	rs151181050	12	51108283	DIP2B	missense	0.002	5	1.24	0.23	5	1.31	0.14	5	1.28	0.17	5	1.27	0.19
exm-rs111695	**G**	**rs11169552**	**12**	**51155663**			0.734	**9**	**1.08**	**2.55E-05**	**6**	**1.02**	**0.35**	**9**	**1.04**	**0.03**	**9**	**1.06**	**3.60E-03**
exm1002721	A	rs1129406	12	51203371	ATF1	coding-synon/splice	0.403	6	1.11	8.27E-09	#N/A	#N/A	#N/A	6	1.15	1.23E-05	6	1.10	2.86E-05
exm1002733	G	rs2230674	12	51208122	ATF1	missense	0.965	8	1.05	0.32	6	1.03	0.53	8	1.03	0.50	8	1.04	0.45
exm-rs1729165	A	rs17291650	12	51213433	ATF1	coding-synon	0.905	9	1.01	0.72	6	0.98	0.50	8	0.98	0.62	9	0.99	0.73

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 8. Results of conditional analysis for 1q41 locus.

								Results of meta-analysis			**Conditional to rs6687758**		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**
exm150731	G	rs115082227	1	221879569	DUSP10	missense	0.9957	4	1.11	0.50	3	1.09	0.54
exm150738	C	rs140139532	1	221879742	DUSP10	missense	0.9998	3	1.22	0.73	3	1.32	0.64
exm150778	C	rs148146409	1	221912959	DUSP10	missense	0.9996	4	1.15	0.78	4	1.29	0.61
exm-rs6687758	**G**	**rs6687758**	**1**	**222164948**			0.1955	**9**	**1.14**	**3.15E-11**	**#N/A**	**#N/A**	**#N/A**
exm-rs873549	A	rs873549	1	222271767			0.7137	9	1.00	0.98	9	0.99	0.60
exm-rs17163128	G	rs17163128	1	222619902			0.1964	6	1.04	0.13	6	1.02	0.29
exm2263851	A	rs11485177	1	222640209			0.5368	6	1.03	0.09	6	1.03	0.10

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 9. Results of conditional analysis for 8q24.21 locus.

								Results of meta-analysis			Conditional to rs16888728			Conditional to rs7014346			Conditional to rs10505477			Conditional to rs10505477 and rs7014346		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N**	**P.fixed**	**OR.fixed**	**N.cond**	**OR.cond**	**P.cond**	**N.cond**	**OR.cond**	**P.cond**	**N.cond**	**OR.cond**	**P.cond**
exm-rs16902094	G	rs16902094	8	128320346			0.141	6	1.01	0.78	6	1.01	0.85	6	0.99	0.73	6	1.01	0.76	6	0.9981	0.9449
exm-rs445114	A	rs445114	8	128323181			0.633	8	1.04	0.02	8	1.02	0.19	8	1.03	0.14	6	1.02	0.29	6	1.0196	0.3201
exm-rs1562430	A	rs1562430	8	128387852			0.571	9	1.01	0.47	9	1.01	0.71	9	1.00	0.93	9	1.01	0.48	9	1.0096	0.5722
exm-rs10505477	**A**	**rs10505477**	**8**	**128407443**	***CASC8***		0.511	**9**	**1.17**	**2.13E-21**	**9**	**0.98**	**0.73**	**9**	**1.12**	**1.57E-05**	**#N/A**	**#N/A**	**#N/A**	**#N/A**	**#N/A**	**#N/A**
exm-rs6983267	**C**	**rs6983267**	**8**	**128413305**	***CASC8***		0.520	**9**	**1.19**	**1.09E-27**	**#N/A**	**#N/A**	**#N/A**	**9**	**1.13**	**2.96E-07**	**9**	**1.21**	**6.07E-03**	**9**	**1.19**	**0.01117**
exm-rs7014346	**A**	**rs7014346**	**8**	**128424792**	***CASC8***		0.376	**9**	**1.17**	**4.20E-24**	**9**	**1.07**	**3.06E-03**	**#N/A**	**#N/A**	**#N/A**	**9**	**1.07**	**8.55E-03**	**#N/A**	**#N/A**	**#N/A**
exm-rs1447295	A	rs1447295	8	128485038			0.100	9	1.05	0.12	9	1.04	0.15	9	1.03	0.36	7	1.04	0.19	7	1.0324	0.2976
exm2270923	C	rs7836840	8	128491792			0.518	6	1.01	0.54	6	1.03	0.14	6	1.02	0.37	6	1.03	0.15	6	1.0243	0.2037
exm-rs4242382	A	rs4242382	8	128517573			0.101	9	1.06	0.06	9	1.05	0.07	9	1.04	0.20	7	1.05	0.09	7	1.0452	0.1477
exm-rs4242384	C	rs4242384	8	128518554			0.100	8	1.05	0.12	8	1.04	0.16	8	1.03	0.35	7	1.06	0.08	7	1.0474	0.1304
exm720579	G	rs146505192	8	128750527	*MYC*	missense	0.001	4	1.16	0.62	4	1.18	0.56	4	1.17	0.59	4	1.18	0.57	4	1.1782	0.5718
exm720581	G	rs4645959	8	128750540	*MYC*	missense	0.040	9	1.01	0.88	9	1.00	0.91	9	1.00	0.97	9	1.03	0.47	9	1.0312	0.4686
exm720620	G	rs200431478	8	128752924	*MYC*	missense	0.9997	3	1.42	0.68	2	1.46	0.65	2	1.46	0.65	2	1.47	0.65	2	1.47	0.6472
exm2266765	A	rs959409	8	128920127			0.998	6	1.01	0.98	6	1.02	0.94	6	1.01	0.98	6	1.02	0.93	6	1.0126	0.9574

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 10. Results of conditional analysis for 15q13.3 locus.

								Results of meta-analysis			**Conditional to rs4779584**		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**
exm1145149	G	rs61733064	15	32925302	*ARHGAP11A*	missense	0.986	6	1.03	0.69	6	1.01	0.87
exm1145205	A	rs34173159	15	32929624	*ARHGAP11A*	missense	0.965	6	1.04	0.40	6	1.03	0.59
exm-rs4779584	**A**	**rs4779584**	**15**	**32994756**			0.188	**9**	**1.19**	**2.3E-18**	**#N/A**	**#N/A**	**#N/A**
exm1145262	G	rs199894051	15	33022968	*GREM1*	missense	0.00018	2	0.81	0.75	2	0.83	0.78
exm1145283	A	rs200979045	15	33091015	*FMN1*	missense	0.999	2	1.74	0.13	2	1.93	0.07
exm2272223	A	rs16959110	15	33106236	*FMN1*	intron	0.264	9	1.04	0.02	9	0.98	0.30
exm1145344	A	rs150962800	15	33260973	*FMN1*	missense	0.024	6	1.04	0.51	6	1.04	0.55
exm1145368	G	rs201216330	15	33261263	*FMN1*	missense	0.999	2	1.43	0.27	2	1.47	0.23

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 11. Results of conditional analysis for 18q21.1 locus.

								Results of meta-analysis			Conditional to rs4939827		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**
exm2268151	G	rs12454113	18	46044052			0.838	6	1.03	0.29	6	1.03	0.31
exm1385990	A	rs2277712	18	46163049	*KIAA0427*	missense	0.034	8	1.05	0.28	8	1.03	0.48
exm1386018	G	rs145237824	18	46284585	*KIAA0427*	missense	0.998	4	1.46	0.10	4	1.41	0.13
exm1386072	G	rs147123396	18	46383972	*KIAA0427*	missense	0.00038	3	1.14	0.77	3	1.01	0.98
exm2273563	A	rs142559064	18	46385959	*KIAA0427*	utr-3	0.008	6	1.09	0.41	6	1.06	0.59
exm-rs4939827	**A**	**rs4939827**	**18**	**46453463**	***SMAD7***	**intron**	0.519	**9**	**1.21**	**1.3E-33**	**#N/A**	**#N/A**	**#N/A**
exm1386154	G	rs142608802	18	46623780	*DYM*	missense	0.00043	2	1.18	0.72	2	1.10	0.83
exm1386166	G	rs138427861	18	46645157	*DYM*	missense	0.998	4	1.16	0.49	4	1.21	0.38
exm-rs11661691	C	rs11661691	18	46770186	*DYM*	intron	0.523	6	1.02	0.29	6	1.02	0.38
exm1386180	G	rs145408029	18	46798603	*DYM*	missense	0.001	4	1.40	0.20	4	1.31	0.30
exm-rs9967417	C	rs9967417	18	46959500	*DYM*	intron	0.435	6	1.02	0.36	6	1.02	0.26
exm2268102	A	rs2156497	18	46976586	*DYM*	intron	0.664	6	1.02	0.38	6	1.02	0.41
exm-rs8099594	A	rs8099594	18	46991160			0.662	6	1.02	0.35	6	1.02	0.38

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 12. Results of conditional analysis for 19q13.11 locus.

								Results of meta-analysis			**Conditional to rs10411210**		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**
exm1453011	G	rs36017455	19	33465099	*C19orf40*	missense	0.99	6	1.02	0.85	6	1.02	0.85
exm1453016	G	rs2304103	19	33467413	*C19orf40*	missense	0.96	6	1.08	0.14	6	1.03	0.51
exm1453018	A	rs141801484	19	33467427	*C19orf40*	missense	0.0003	3	1.09	0.88	3	1.07	0.91
exm1453024	A	rs3816032	19	33467515	*C19orf40*	missense	0.90	9	1.03	0.28	9	1.01	0.62
exm1453027	G	rs148106526	19	33467575	*C19orf40*	missense	1.00	4	1.35	0.15	4	1.31	0.20
exm-rs10411210	**G**	**rs10411210**	**19**	**33532300**	***RHPN2***	**intron**	0.91	**9**	**1.18**	**2.4E-08**	**#N/A**	**#N/A**	**#N/A**
exm1453177	A	rs148710327	19	33584313	*GPATCH1*	missense	0.0004	2	1.62	0.29	2	1.59	0.30
exm1453180	G	rs150894192	19	33584352	*GPATCH1*	missense	0.9991	4	1.24	0.55	4	1.25	0.53
exm1453218	G	rs139753668	19	33588770	*GPATCH1*	missense	0.0010	4	1.21	0.48	4	1.19	0.52
exm1453236	A	rs2287679	19	33600764	*GPATCH1*	missense	0.75	6	1.02	0.47	6	0.96	0.14
exm1453272	C	rs143082587	19	33604701	*GPATCH1*	missense	0.0013	2	1.22	0.43	2	1.21	0.46
exm1453308	G	rs73039449	19	33616077	*GPATCH1*	missense	0.99	6	1.13	0.20	6	1.11	0.28

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 13. Results of conditional analysis for 20p12.3 locus.

								Results of meta-analysis			Conditional to rs961253		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**
exm1524404	G	rs2232078	20	6064805	*FERMT1*	missense	0.99	6	1.11	0.39	6	1.10	0.42
exm1524408	G	rs2232074	20	6065729	*FERMT1*	missense	0.63	6	1.02	0.30	6	1.02	0.30
exm1524416	G	rs145202913	20	6065922	*FERMT1*	missense	0.9990	3	1.17	0.64	3	1.14	0.70
exm2254361	G	rs35413391	20	6069723	*FERMT1*	coding-synon	0.93	6	1.09	0.03	6	1.08	0.03
exm1524442	A	rs202037230	20	6078265	*FERMT1*	missense	0.00023	2	2.01	0.16	2	2.01	0.16
exm1524451	G	rs55666319	20	6090969	*FERMT1*	missense	0.05	6	1.04	0.31	6	1.05	0.25
exm1524465	A	rs16991866	20	6093177	*FERMT1*	missense	0.90	8	1.04	0.20	8	1.04	0.15
exm-rs961253	**A**	**rs961253**	**20**	**6404281**			0.36	**9**	**1.12**	**6.8E-12**	**#N/A**	**#N/A**	**#N/A**
exm1524497	A	rs2273073	20	6750882	*BMP2*	missense	0.98	6	1.07	0.38	6	1.08	0.28

Variants used for conditional analysis are shaded grey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 14. Results of conditional analysis for 20q13.33 locus.

								Results of meta-analysis			Conditional to rs4925386		
SNP	**A1**	**RsID**	**CHR**	**BP**	**PPgene**	**Annotation**	**EAF**	**N**	**OR.fixed**	**P.fixed**	**N.cond**	**OR.cond**	**P.cond**
exm1555380	A	rs140197067	20	60884852	*LAMA5*	missense	0.0113	6	1.19	0.04	6	1.15	0.10
exm1555390	A	rs41310831	20	60885119	*LAMA5*	missense	0.0022	5	1.28	0.17	5	1.24	0.23
exm1555393	G	rs139502000	20	60885242	*LAMA5*	missense	0.9944	6	0.99	0.94	6	1.01	0.97
exm1555398	G	rs146516865	20	60885275	*LAMA5*	missense	0.9994	2	1.30	0.58	2	1.35	0.53
exm1555403	A	rs41307203	20	60885362	*LAMA5*	missense	0.0237	6	1.02	0.71	6	0.99	0.87
exm2234682	A	rs200093098	20	60885845	*LAMA5*	missense	0.0002	2	2.23	0.39	2	2.16	0.41
exm1555432	A	rs147595855	20	60886106	*LAMA5*	missense	0.9996	2	1.40	0.55	2	1.41	0.54
exm1971015	A	rs112963711	20	60886272	*LAMA5*	missense	0.0008	4	1.00	1.00	4	1.08	0.82
exm1555461	A	rs142756912	20	60886683	*LAMA5*	missense	0.0007	3	1.58	0.13	3	1.53	0.16
exm1971028	A	rs201837442	20	60887030	*LAMA5*	missense	0.0001	2	1.42	0.68	2	1.36	0.72
exm1555486	A	rs147777385	20	60887230	*LAMA5*	missense	0.0004	2	2.17	0.07	2	2.27	0.05
exm1555488	A	rs140181393	20	60887239	*LAMA5*	missense	0.0235	6	1.03	0.61	6	1.00	0.97
exm1555503	G	rs149357675	20	60887356	*LAMA5*	missense	0.9962	4	1.29	0.14	4	1.32	0.10
exm1555538	A	rs148336880	20	60888018	*LAMA5*	missense	0.999	2	4.32	0.05	2	4.40	0.04
exm1555563	A	rs138708242	20	60888510	*LAMA5*	missense	0.01	6	1.04	0.77	6	1.00	0.98
exm1555588	A	rs150774821	20	60889493	*LAMA5*	missense	0.9996	2	1.85	0.33	2	1.91	0.30
exm1555634	A	rs141753663	20	60890155	*LAMA5*	missense	0.0004	2	2.00	0.07	2	2.12	0.05
exm1555643	G	rs201926183	20	60890262	*LAMA5*	coding-synon	0.9996	2	1.41	0.54	2	1.28	0.66
exm1555702	A	rs140777270	20	60892813	*LAMA5*	missense	0.0011	3	1.37	0.23	3	1.32	0.30
exm1555706	A	rs201111971	20	60893527	*LAMA5*	missense	0.0001	2	4.20	0.12	2	3.91	0.14
exm1555718	G	rs150998056	20	60893611	*LAMA5*	missense	0.9996	2	1.53	0.62	2	1.57	0.60
exm1555735	A	rs147290767	20	60893697	*LAMA5*	missense	0.0029	5	1.11	0.51	5	1.19	0.29
exm1555779	A	rs140781444	20	60895806	*LAMA5*	missense	0.0002	2	1.45	0.67	2	1.45	0.67
exm1555786	G	rs139401504	20	60895865	*LAMA5*	missense	0.9988	4	1.14	0.67	4	1.18	0.59
exm1555804	A	rs141208202	20	60897104	*LAMA5*	missense	0.04	6	1.09	0.05	6	1.06	0.23
exm1555826	A	rs200678763	20	60897453	*LAMA5*	missense	0.0005	2	2.20	0.04	2	2.11	0.05
exm1555881	G	rs141989486	20	60899224	*LAMA5*	missense	0.9987	4	1.18	0.57	3	1.08	0.79
exm1555885	C	rs148177752	20	60899513	*LAMA5*	missense	0.99	4	0.99	0.92	6	1.03	0.82
exm1555893	A	rs142055388	20	60900388	*LAMA5*	missense	0.0032	4	1.19	0.25	4	1.30	0.09
exm1555901	A	rs2427284	20	60900481	*LAMA5*	missense	0.05	6	1.04	0.31	6	1.14	1.88E-03
exm1555902	A	rs149570905	20	60900490	*LAMA5*	missense	0.00018	2	1.87	0.36	2	1.81	0.39
exm1555914	A	rs139530736	20	60900593	*LAMA5*	missense	0.00008	2	1.42	0.68	2	1.41	0.69
exm1555919	A	rs11699758	20	60901762	*LAMA5*	missense	0.03	6	1.03	0.59	6	1.12	0.03
exm1555925	G	rs149220558	20	60901785	*LAMA5*	missense	0.9994	3	1.52	0.37	3	1.40	0.47
exm1555929	A	rs45496002	20	60901932	*LAMA5*	missense	0.01	6	1.08	0.41	6	1.04	0.64
exm1555934	A	rs875379	20	60901986	*LAMA5*	missense	0.09	9	1.05	0.08	9	1.01	0.59
exm1555939	A	rs150196385	20	60902022	*LAMA5*	missense	0.0003	2	1.76	0.19	2	1.70	0.21
exm1555946	G	rs34000043	20	60902366	*LAMA5*	missense	0.99	4	1.21	0.04	5	1.13	0.20
exm1555957	A	rs199963174	20	60902604	*LAMA5*	missense	0.00038	2	1.38	0.43	2	1.31	0.51
exm1556005	A	rs144368979	20	60904031	*LAMA5*	missense	0.00064	3	1.05	0.90	3	1.03	0.94
exm1556030	A	rs150741810	20	60905559	*LAMA5*	missense	0.00041	2	1.24	0.66	2	1.16	0.76
exm1556058	A	rs201679986	20	60906148	*LAMA5*	missense	0.00023	2	1.44	0.51	2	1.41	0.54
exm1556077	A	rs138521932	20	60907761	*LAMA5*	missense	0.01	4	1.14	0.29	4	1.23	0.10
exm1556106	G	rs13042941	20	60908969	*LAMA5*	missense	0.93	6	1.01	0.75	6	0.92	0.04
exm1556143	A	rs79319629	20	60910124	*LAMA5*	missense	0.97	6	1.06	0.28	6	1.10	0.09
exm1556159	A	rs201119098	20	60911471	*LAMA5*	missense	0.0004	2	1.09	0.86	2	1.05	0.92
exm1556196	A	rs199759497	20	60912983	*LAMA5*	missense	0.0008	3	1.72	0.06	3	1.66	0.08
exm-rs4925386	**G**	**rs4925386**	**20**	**60921044**	***LAMA5***	**intron**	0.68	**9**	**1.11**	**8.676E-10**	**#N/A**	**#N/A**	**#N/A**
exm1556277	A	rs78026347	20	60926766	*LAMA5*	missense	0.01	4	1.09	0.48	4	1.18	0.19
exm1556279	A	rs114928407	20	60926772	*LAMA5*	missense	0.0005	2	1.06	0.89	2	1.01	0.98
exm1556360	A	rs111872483	20	60963386	*RPS21*	missense	0.0004	2	1.44	0.38	2	1.53	0.30
exm1556410	A	rs143243918	20	60968561	*CABLES2*	missense	0.0006	2	1.31	0.45	2	1.27	0.50
exm1556432	G	rs41284974	20	60971397	*CABLES2*	missense	0.9934	5	1.28	0.06	5	1.19	0.18
exm1556470	G	rs141000397	20	60985999	*C20orf151*	missense	0.9998	2	1.04	0.95	2	1.03	0.97
exm1556471	A	rs2236200	20	60986019	*C20orf151*	missense	0.75	9	1.08	3.60E-05	9	1.03	0.10
exm1556479	G	rs138112542	20	60987715	*C20orf151*	missense	0.99960	2	1.27	0.66	2	1.33	0.60
exm1556489	A	rs141215868	20	60987888	*C20orf151*	missense	0.00028	3	1.28	0.67	3	1.31	0.65

ey. Previously described GWAS variant(s) are higlighted using bold font.

Supplementary Table 15. Relationship between rs1129406 *(ATF1,* 12q13), rs12303082 *(FAM186A,* 12q13), rs6580742 *(FAM186A,* 12q13), rs16888728 *(UTP23,* 8q24) and rs3184504 *(SH2B3* , 12q24) genotypes and sex, age at diagnosis of CRC, tumour site (rectal [ICD9:154], colonic [ICD9:153]), stage and MSI status.

		Age			**Gender**			**Site**			**MSI**			**Stage (Invasive vs Non Invasive)**		
		OR(95% CI)	**p value**	**Sample Size**	**OR(95% CI)**	**p value**	**Sample Size**	**OR(95% CI)**	**p value**	**Sample Size**	**OR(95% CI)**	**p value**	**Sample Size**	**OR(95% CI)**	**p value**	**Sample Size**
rs1129406	exm1002721	0.998 (0.993-1.003)	0.42	5410	1.059 (0.974-1.152)	0.18	7964	0.984 (0.886-1.093)	0.77	5281	0.998 (0.993-1.003)	0.85	213	0.998 (0.993-1.003)	0.40	4280
rs12303082	exm1002434	0.996 (0.991-1)	0.06	5410	1.044 (0.96-1.135)	0.31	8160	0.995 (0.896-1.106)	0.93	5281	0.996 (0.991-1)	0.76	213	0.996 (0.991-1)	0.44	4280
rs6580742	exm1002264	0.997 (0.992-1.002)	0.18	5410	1.053 (0.964-1.15)	0.25	8461	0.97 (0.866-1.087)	0.60	5281	0.997 (0.992-1.002)	0.88	213	0.997 (0.992-1.002)	0.53	4280
rs16888728	exm716877	0.993 (0.988-0.999)	0.03	5410	1.209 (1.085-1.345)	5.6E-04	8160	0.98 (0.855-1.124)	0.77	5281	0.993 (0.988-0.999)	0.34	213	0.993 (0.988-0.999)	0.42	4280
rs3184504	exm1037423	1.001 (0.997-1.006)	0.53	5410	1.005 (0.926-1.09)	0.91	8459	0.924 (0.832-1.026)	0.14	5281	1.001 (0.997-1.006)	0.28	213	1.001 (0.997-1.006)	0.13	4280

* Test is significant after correction for multiple testing (p<0.05/25)

Supplementary Table 16. Characteristics and genotype counts of SNPs within *PRAMEF12* and *MALRD1*

Gene	rs-number	Position	A1	A2	N of genotypes in cases	N of genotypes in controls	OR	P for Fisher Exact Test
PCDHGA1	rs201832666	chr5:140790128	A	C	0/0/6903	0/3/21916	0	0.5681
PCDHGA2	rs111794989	chr5:140763615	A	C	0/58/6849	0/103/21821	1.587	0.005863
PCDHGA3	rs182127695	chr5:140795143	G	A	0/2/6905	0/5/21919	1.077	1
PCDHGA4	rs6878145	chr5:140718552	G	A	0/1/6906	0/2/21923	1.347	1
PCDHGB1	rs144548345	chr5:140718897	G	A	0/7/6900	0/15/21908	1.257	0.6331
	rs17097185	chr5:140711097	C	G	0/1/6906	0/2/21919	1.347	1
	rs200981359	chr5:140718994	C	A	0/1/6906	0/2/21923	1.347	1
	rs201553091	chr5:140719317	A	G	0/0/6907	0/2/21923	0	1
	rs200811046	chr5:140719478	G	A	0/1/6906	0/3/21922	0.8979	1
	rs144241311	chr5:140719556	A	G	0/22/6885	0/45/21880	1.437	0.1742
	rs143727841	chr5:140719633	G	A	0/1/6906	0/9/21902	0.2991	0.3051
	rs199852408	chr5:140720144	A	C	0/6/6901	0/16/21908	1.01	1
	rs186274609	chr5:140724879	A	G	0/11/6896	0/22/21903	1.406	0.3435
	rs200604016	chr5:140725033	T	A	0/16/6891	0/47/21877	1.291	0.349
	rs201709248	chr5:140726055	C	A	0/1/6906	0/2/21923	1.347	1
	rs76289268	chr5:140730210	A	G	0/0/6907	0/2/21922	0	1
	rs199977912	chr5:140730489	A	G	0/9/6898	0/37/21888	0.9464	1
	rs77250251	chr5:140731022	G	A	7/393/6507	17/1163/20744	1.058	0.314
	rs200777796	chr5:140732220	A	C	0/12/6895	0/22/21902	1.592	0.1852
	rs146402451	chr5:140734802	G	C	0/32/6875	0/82/21840	1.183	0.4073
	rs201855847	chr5:140735405	A	C	0/0/6902	0/6/21910	0	0.2001
	rs201518165	chr5:140739812	G	A	0/3/6904	0/13/21908	1.036	1
	rs150944400	chr5:140740021	A	G	1/0/6906	0/2/21922	4.041	0.1266
	rs62621827	chr5:140740060	A	G	0/2/6905	0/2/21923	2.695	0.297
	rs201960802	chr5:140742092	A	C	0/0/6905	0/4/21919	0	0.58
	rs144886424	chr5:140744055	A	G	0/5/6902	0/8/21917	2.021	0.2262
	rs199512708	chr5:140744841	G	A	0/7/6900	0/15/21908	1.796	0.1749
	rs200032836	chr5:140745129	C	A	0/13/6894	0/33/21890	1.304	0.4078
	rs201155008	chr5:140750439	A	G	0/1/6906	0/7/21914	0.3847	0.6913
	rs116495533	chr5:140750460	C	G	0/3/6904	0/3/21921	2.694	0.3539
	rs199674539	chr5:140750710	G	A	0/1/6906	0/7/21916	0.4489	0.6825
	rs201701201	chr5:140750849	C	A	0/3/6904	0/8/21917	1.539	0.5028
	rs199851082	chr5:140750868	G	A	0/3/6904	0/5/21918	2.155	0.2649
	rs200031435	chr5:140751096	G	A	0/7/6900	0/16/21907	1.179	0.8144
	rs201408759	chr5:140752321	A	G	0/13/6894	0/43/21882	1.476	0.1613
	rs201390749	chr5:140753970	G	A	0/11/6896	0/22/21903	1.347	0.4344
	rs11575955	chr5:140755901	A	C	0/270/6636	0/788/21132	1.119	0.09463
	rs148240637	chr5:140763317	A	T	0/3/6904	0/3/21908	2.693	0.354
	rs141242913	chr5:140763370	G	A	0/9/6898	0/24/21900	1.235	0.5698
	rs201582947	chr5:140763490	A	C	0/0/6907	0/12/21908	0.4488	0.3771
	rs199642192	chr5:140763515	G	C	0/0/6907	0/7/21912	0	0.201
	rs185786686	chr5:140763665	G	A	2/160/6745	0/399/21526	1.29	0.004516
	rs200109598	chr5:140768308	C	A	0/7/6900	0/28/21895	1.347	0.3854
	rs144915863	chr5:140768676	A	G	0/6/6901	0/17/21907	1.109	0.8195
	rs202220616	chr5:140768767	G	A	0/20/6887	0/52/21872	1.057	0.791
	rs199638280	chr5:140769438	C	G	0/5/6902	0/5/21920	2.694	0.1472
	rs113280752	chr5:140772736	G	A	0/26/6881	0/74/21851	1.123	0.5786
	rs201697840	chr5:140773461	C	G	0/20/6887	0/55/21867	1.047	0.8966
	rs115102808	chr5:140773738	A	G	1/202/6704	3/611/21309	1.064	0.4169
	rs116789057	chr5:140774403	C	A	0/2/6905	0/1/21923	1.796	0.6171
	rs201846904	chr5:140778163	A	G	0/23/6884	1/35/21889	1.676	0.05819
	rs150385715	chr5:140778259	G	A	0/26/6881	0/87/21838	1.053	0.8377
	rs202099773	chr5:140782608	G	A	0/1/6906	0/3/21922	0.898	1
	rs199643799	chr5:140783490	A	C	0/27/6880	0/48/21877	1.629	0.04024
	rs200620626	chr5:140784038	G	A	0/4/6903	0/10/21915	1.078	1
	rs145718404	chr5:140784495	A	G	0/0/6907	0/2/21923	1.347	1
	rs200974828	chr5:140784636	A	G	0/1/6906	1/14/21909	0.1584	0.0582
	rs17097274	chr5:140784892	C	G	0/2/6905	0/1/21922	1.796	0.6171
	rs115772303	chr5:140788731	A	G	0/0/6907	0/8/21917	0	0.201
	rs186373896	chr5:140788965	G	A	0/2/6905	0/0/21923	NA	0.0733
	rs199531162	chr5:140789304	G	C	0/20/6887	0/64/21860	0.8843	0.7203
	rs201698858	chr5:140789981	A	G	0/0/6905	0/4/21918	0	0.3328
	rs6891442	chr5:140790092	C	A	0/4/6903	0/3/21922	3.592	0.09126
	rs11575962	chr5:140794963	A	G	0/32/6749	0/79/21630	1.244	0.2914
	rs200868391	chr5:140795153	A	G	0/5/6902	0/14/21910	0.962	1
	rs201327680	chr5:140798669	G	A	0/2/6905	0/4/21921	2.021	0.3974
	rs185228661	chr5:140798742	A	C	0/0/6907	0/2/21923	0	1
	rs200899065	chr5:140799306	A	G	0/2/6905	0/7/21918	0.7696	1
	rs200342957	chr5:140801897	A	G	0/16/6891	0/26/21897	1.697	0.09058
	rs199795822	chr5:140802002	G	A	0/3/6904	0/6/21918	1.347	0.7105
	rs199507728	chr5:140802374	A	G	0/13/6894	0/32/21893	1.094	0.74
	rs141810253	chr5:140803055	G	A	0/8/6896	0/20/21890	1.616	0.2305
	rs114008539	chr5:140803260	A	C	0/2/6905	0/5/21918	0.8978	1
	rs143083513	chr5:140810655	G	A	0/3/6904	0/4/21919	2.02	0.3974
	rs150444699	chr5:140856212	G	A	0/2/6905	0/6/21919	0.8979	1
	rs140933475	chr5:140856972	A	G	0/8/6899	0/16/21909	1.617	0.2546
	rs114678203	chr5:140864858	A	C	0/4/6903	0/10/21915	1.617	0.3982
	rs76923861	chr5:140865264	G	A	5/348/6554	16/1017/20891	1.081	0.1815
	rs144347539	chr5:140866832	C	G	0/83/6824	2/218/21700	1.085	0.5218
	rs201458212	chr5:140867006	T	A	0/1/6906	0/8/21916	0.3367	0.4598
	rs116370895	chr5:140867061	A	C	0/11/6896	0/41/21883	0.9669	1
	rs115565444	chr5:140867087	A	G	0/1/6906	0/4/21921	0.6734	1
	rs151293422	chr5:140867123	G	A	0/10/6897	1/26/21898	1.058	0.8579
	rs199722860	chr5:140867277	A	G	0/8/6899	0/16/21904	1.616	0.2547
	rs2233601	chr5:140869229	A	G	0/4/6903	0/12/21913	1.122	0.789
	rs2233603	chr5:140869630	A	G	0/2/6905	0/2/21923	2.021	0.3974
	rs141484080	chr5:140870165	A	G	0/3/6904	0/7/21916	1.154	0.7361
	rs201409669	chr5:140870270	A	G	0/5/6902	0/12/21912	1.347	0.5965
	rs141959335	chr5:140870828	G	A	0/1/6906	0/5/21920	0	0.58
	rs200418116	chr5:140874422	A	G	0/2/6905	0/2/21923	1.796	0.6171
	rs61749029	chr5:140890616	A	G	0/5/6902	0/7/21918	3.08	0.03657

Supplementary Table 17. Gene Ontology (GO) enrichment analysis.

GO Term	Description	P-value	FDR q-value	Enrichment (=(b/n) / (B/N))	Total number of genes	Total number of genes associated with a specific GO term	Number of genes in the top of the user's input list	Number of genes in the intersection	Genes
GO:0007156	homophilic cell adhesion via plasma membrane adhesion molecules	2.36E-24	2.93E-20	20.57	11710	133	107	25	[PCDHA8, PCDHA7, PCDHA6, PCDHA5, PCDHA4, PCDHA3, PCDHA2, PCDHA1, PCDHGB3, PCDHGB2, PCDHGB1, CELSR2, PCDHGB5, CADM3, PCDHGA7, PCDHGA6, PCDHGA3, PCDHGA2, PCDHGA5, PCDHGA4, PCDHGA1, FAT3, PCDHB1, PCDHB8, FAT1]
GO:0098742	cell-cell adhesion via plasma-membrane adhesion molecules	8.46E-22	5.25E-18	16.58	11710	165	107	25	[PCDHA8, PCDHA7, PCDHA6, PCDHA5, PCDHA4, PCDHA3, PCDHA2, PCDHA1, PCDHGB3, PCDHGB2, PCDHGB1, CELSR2, PCDHGB5 , CADM3 , PCDHGA7, PCDHGA6 , PCDHGA3, PCDHGA2, PCDHGA5, PCDHGA4, PCDHGA1, FAT3 , PCDHB1 , PCDHB8, FAT1]
GO:0098609	cell-cell adhesion	8.03E-17	3.32E-13	9.27	11710	406	84	27	[PCDHA8 , PCDHA7 , PCDHA6 , PCDHA5, PCDHA4, PCDHA3, PCDHA2, PCDHA1 , PCDHGB3 , PCDHGB2 , PCDHGB1 , GPR98 , CELSR2 , PCDHGB5, CLIC1, PCDHGA7, PCDHGA6 , PCDHGA3, PCDHGA2 , PCDHGA5 , PCDHGA4, PCDHGA1, FAT3, PCDHB1, IRF4, IL7R, FAT1]
GO:0007155	cell adhesion	4.09E-13	1.27E-09	5.61	11710	727	89	31	[PCDHA8, PCDHA7, PCDHA6, PCDHA5, PCDHA4, PCDHA3, PCDHA2, PCDHA1, HEPACAM, PCDHGB3, PCDHGB2, ITGB6, PCDHGB1, GPR98, CELSR2 , PCDHGB5, CLIC1, PCDHGA7, PCDHGA6, PCDHGA3, PCDHGA2, PCDHGA5, PCDHGA4 , PCDHGA1, SLAMF7, FAT3, PCDHB1, IRF4, IL7R, COL17A1, FAT1]
GO:0022610	biological adhesion	4.26E-13	1.06E-09	5.6	11710	728	89	31	[PCDHA8 8, PCDHA7, PCDHA6, PCDHA5, PCDHA4, PCDHA3, PCDHA2, PCDHA1, HEPACAM, PCDHGB3, ITGB6, PCDHGB2, PCDHGB1, GPR98, CELSR2, PCDHGB5, CLIC1, PCDHGA7, PCDHGA6, PCDHGA3, PCDHGA2, PCDHGA5 , PCDHGA4, PCDHGA1, SLAMF7, FAT3, PCDHB1, IRF4 IL7R , COL17A1, FAT1]
GO:0007399	nervous system development	5.75E-06	1.19E-02	7.37	11710	169	94	10	[PCDHA8, PCDHA7, GPR98, PCDHA6, PCDHA5, EP300, PCDHA4, PCDHA3, PCDHA2, PCDHA1]
GO:2000400	positive regulation of thymocyte aggregation	1.71E-05	3.03E-02	16.6	11710	8	441	5	[RASGRP1, GLI2, TESPA1, IL7R, VNN1]
GO:0033089	positive regulation of T cell differentiation in thymus	1.71E-05	2.65E-02	16.6	11710	8	441	5	[RASGRP1, GLI2, TESPA1, IL7R, VNN1]
GO:0001539	cilium or flagellum-dependent cell motility	2.44E-05	3.37E-02	8.05	11710	11	926	7	[DNAH17, DNAH3, DNAH1, DRC1, DNAH7, DNAH8, DNAH6]
GO:0007018	microtubule-based movement	8.23E-05	1.02E-01	2.92	11710	155	518	20	[DNAH17 , KIF14, NDE1, TTC21A, STK36, KIF15, KIF21B, DNAH11, RASGRP1, IFT74, DNHD1, KIF26A, DNAH1, CELSR2, STARD9, IFT122, DNAH8, DNAH6, HEATR2, KIF27]
GO:0060989	lipid tube assembly involved in organelle fusion	8.54E-05	9.64E-02	11,710.00	11710	1	1	1	[PCDHGA3]
GO:0048731	system development	1.08E-04	1.12E-01	3.89	11710	426	99	14	[MAPK9, PCDHA8, PCDHA7, PCDHA6, PCDHA5, PCDHA4, PCDHA3, PCDHA2, PCDHA1, GPR98, KIF26A , EP300, CELSR2, SH3GL1]
GO:0021914	negative regulation of smoothened signaling pathway involved in ventral spinal cord patterning	2.01E-04	1.92E-01	21.25	11710	3	551	3	[TULP3, IFT122, RFX4]
GO:0021952	central nervous system projection neuron axonogenesis	2.88E-04	2.55E-01	6.01	11710	14	974	7	[PAFAH1B1, MYCBP2, GLI2, SZT2, CDH11, EPHB2, PLXNA4]
GO:2000398	regulation of thymocyte aggregation	2.95E-04	2.44E-01	6.61	11710	20	620	7	[RASGRP1, GLI2, TESPA1, IL7R, BMP4, SOS2, VNN1]
GO:0033081	regulation of T cell differentiation in thymus	2.95E-04	2.29E-01	6.61	11710	20	620	7	[RASGRP1, GLI2, TESPA1, IL7R, BMP4, SOS2, VNN1]
GO:0048625	myoblast fate commitment	3.66E-04	2.67E-01	70.54	11710	2	166	2	[TCF7L2, EPAS1]
GO:0021955	central nervous system neuron axonogenesis	4.47E-04	3.08E-01	5.06	11710	19	974	8	[PAFAH1B1, MYCBP2, GLI2, SZT2, CDH11, EPHB2, NDEL1, PLXNA4]
GO:0006427	histidyl-tRNA aminoacylation	6.90E-04	4.51E-01	52.75	11710	2	222	2	[HARS2, HARS]
GO:0060988	lipid tube assembly	7.47E-04	4.64E-01	3,903.33	11710	3	1	1	[PCDHGA3]

The system has recognized 12826 genes out of 16584 gene terms entered by the user.

0 genes were recognized by gene symbol and 12826 genes by other gene IDs .

1 duplicate genes were removed (keeping the highest ranking instance of each gene) leaving a total of 12825 genes.

Only 11710 of these genes are associated with a GO term.

Supplementary Table 18. (1) Candidate dominant high-penetrance CRC alleles; (2) Candidate recessive high-penetrance CRC alleles.

(1) Dominant high-penetrance alleles

SNP	RsID	Gene	Mutation	Position	AFF	UNAFF	P	A1	A2	ALL.cases	ALL.controls	ENGLAND.cases	ENGLAND.controls	Scotland.cases	Scotland.controls	PORTUGAL.cases	PORTUGAL.controls	HOLLAND.cases	HOLLAND.controls	SPAIN.cases	SPAIN.controls	GERMANY.cases	GERMANY.controls	pp_score_mean	pp_score_mean_predic	SIFT_score	SIFT_prediction	SIFT_cons	SIFT_OMIM	pp_SIFT_agree	seattle_function_first	anno_type	ExAC freq (EUR,non-Finnish)*
Stop mutations																																	
exm1440289	rs199995129	*NWD1*	Nonsense_R1390X	chr19:16918828	4/8096	0/21819	0.00537	A	G	0/4/8096	0/0/21819	0/3/3581	0/0/10590	0/1/3417	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	0.0001499
exm112227	rs149019370	*CD1A*	Nonsense_W31X	chr1:158224908	3/8097	0/21817	0.01984	A	G	0/3/8097	0/0/21817	0/1/3583	0/0/10590	0/1/3417	0/0/9347	0/0/195	0/0/178	0/1/396	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	0.0002098
exm1283459	rs199641371	*ZNF594*	Nonsense_Q230X	chr17:5086864	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/0/3584	0/0/10590	0/3/3415	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	1.50E-05
exm1295619	rs200681631	*DNAH9*	Nonsense_Y1573X	chr17:11597289	3/8097	0/21819	0.01984	C	A	0/3/8097	0/0/21819	0/1/3583	0/0/10590	0/0/3418	0/0/9349	0/0/195	0/0/178	0/1/396	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	n/a
exm1515136	rs113587027	*ZNF418*	Nonsense_R664X	chr19:58437559	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/2/3582	0/0/10590	0/1/3417	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	0
exm347715	rs201216056	*ABTB1*	Nonsense_C188X	chr3:127395847	3/8097	0/21816	0.01984	A	T	0/3/8097	0/0/21816	0/0/3584	0/0/10590	0/3/3415	0/0/9346	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	3.08E-05
exm521348	rs181930473	*HIST1H3A*	Nonsense_Q69X	chr6:26020922	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/0/3584	0/0/10590	0/0/3418	0/0/9350	0/3/192	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	N/A
Missense mutations																																	
exm682789	rs138438915	*CTSB*	Missense_V249L	chr8:11704609	6/8094	0/21819	0.00039	A	C	0/6/8094	0/0/21819	0/6/3578	0/0/10590	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	1	probably damaging	0.02	DAMAGING	2.86	0	2	missense	nonsynonymous//	0.0001799
exm513693	rs9503910	*C6orf201*	Missense_D25Y	chr6:4087948	5/8094	0/21819	0.00145	A	C	0/5/8094	0/0/21819	0/1/3582	0/0/10589	0/1/3417	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/3/256	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING *Warning! Low confidence.	3.47	0	NA	missense	nonsynonymous//	7.50E-05
exm126316	rs146602337	*SEC16B*	Missense_R142W	chr1:177934291	5/8095	0/21819	0.00145	A	G	0/5/8095	0/0/21819	0/0/3584	0/0/10590	0/1/3417	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/3/256	0/0/273	0/1/246	0/0/1053	0.878	possibly damaging	0.02	DAMAGING	2.25	0	NA	missense	nonsynonymous//	7.86E-05
exm2237096	rs35038757	*STK36*	Missense_R240W	chr2:219543924	5/8095	0/21819	0.00145	A	G	0/5/8095	0/0/21819	0/0/3584	0/0/10590	0/5/3413	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.976	probably damaging	0.02	DAMAGING	2.78	0	2	missense	nonsynonymous//	1.50E-05
exm1169305	rs200881596	*PIF1*	Missense_R327W	chr15:65113473	5/8093	0/21803	0.00146	A	G	0/5/8093	0/0/21803	0/3/3579	0/0/10574	0/0/3418	0/0/9349	0/1/194	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	0.999	probably damaging	0	DAMAGING	2	0	2	missense	nonsynonymous//	0.000135
exm609279	rs146913158	*FAM126A*	Missense_Y64C	chr7:23018030	5/8095	0/21800	0.00146	G	A	0/5/8095	0/0/21800	0/0/3584	0/0/10590	0/5/3413	0/0/9330	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING	2.49	0	2	missense	nonsynonymous//	0.002269 (1)
exm1049488	rs1472840	*NCOR2*	Missense_T2199P	chr12:124817806	4/8092	0/21819	0.00536	C	A	0/4/8092	0/0/21819	0/0/3584	0/0/10590	0/1/3413	0/0/9349	0/1/194	0/0/178	0/0/397	0/0/376	0/2/257	0/0/273	0/0/247	0/0/1053	0.998	probably damaging	0.01	DAMAGING	2.94	0	2	missense	nonsynonymous//	0.0001856
exm141256	rs201947927	*MDM4*	Missense_S367L	chr1:204518437	4/8094	0/21819	0.00537	A	G	0/4/8094	0/0/21819	0/1/3582	0/0/10590	0/0/3417	0/0/9349	0/2/193	0/0/178	0/1/396	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.999	probably damaging	0.03	DAMAGING	2.43	0	2	missense	nonsynonymous//	7.49E-05
exm97036	rs115192275	*CGN*	Missense_V333M	chr1:151492912	4/8095	0/21820	0.00537	A	G	0/4/8095	0/0/21820	0/4/3580	0/0/10590	0/0/3417	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.808	possibly damaging	0	DAMAGING	2.73	0	NA	missense	nonsynonymous//	0.0001199
exm1292157	rs140252285	*KRBA2*	Missense_Q33P	chr17:8274755	4/8095	0/21818	0.00537	C	A	0/4/8095	0/0/21818	0/2/3582	0/0/10590	0/0/3417	0/0/9348	0/0/195	0/0/178	0/1/396	0/0/376	0/0/259	0/0/273	0/1/246	0/0/1053	0.804	possibly damaging	0	DAMAGING *Warning! Low confidence.	3.3	0	NA	missense	nonsynonymous//	0.0002547
exm1435795	rs143659792	*EMR2*	Missense_G604S	chr19:14862462	4/8095	0/21817	0.00537	A	G	0/4/8095	0/0/21817	0/0/3584	0/0/10589	0/4/3414	0/0/9348	0/0/195	0/0/178	0/0/397	0/0/376	0/0/258	0/0/273	0/0/247	0/0/1053	0.845	possibly damaging	0.01	DAMAGING	2.31	0	NA	missense	nonsynonymous//	0
exm1607651	rs201526262	*MICALL1*	Missense_R852C	chr22:38336799	4/8096	0/21820	0.00537	A	G	0/4/8096	0/0/21820	0/2/3582	0/0/10590	0/1/3417	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	0.998	probably damaging	0.01	DAMAGING	3.11	0	2	missense	nonsynonymous//	0
exm39241	rs77828190	*SERINC2*	Missense_R454H	chr1:31907027	4/8096	0/21820	0.00537	A	G	0/4/8096	0/0/21820	0/0/3584	0/0/10590	0/2/3416	0/0/9350	0/2/193	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.913	possibly damaging	0.01	DAMAGING	2.77	0	NA	missense	nonsynonymous//	1.51E-05
exm882861	rs61735506	*OR51B5*	Missense_S295R	chr11:5461860	4/8096	0/21819	0.00537	C	A	0/4/8096	0/0/21819	0/1/3583	0/0/10590	0/1/3417	0/0/9349	0/1/194	0/0/178	0/1/396	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.994	probably damaging	0.01	DAMAGING	2.85	0	2	missense	nonsynonymous//	0.0001949
exm1276720	rs146563186	*MNT*	Missense_A348V	chr17:2290901	4/8096	0/21817	0.00537	A	G	01/03/8096	0/0/21817	0/0/3584	0/0/10590	01/03/3414	0/0/9347	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.982	probably damaging	0.04	DAMAGING	3.13	0	2	missense	nonsynonymous//	1.51E-05
exm159002	rs34622148	*TSNAX-DISC1*	Missense_L330F	chr1:231830492	3/8096	0/21819	0.01983	A	G	0/3/8096	0/0/21819	0/0/3584	0/0/10590	0/1/3416	0/0/9349	0/1/194	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/1/246	0/0/1053	0.999	probably damaging	0.01	DAMAGING	2.87	1	2	missense	nonsynonymous//	3.09E-05
exm434525	rs143573166	*CEP44*	Missense_K119T	chr4:175224972	3/8094	0/21813	0.01983	C	A	0/3/8094	0/0/21813	0/1/3582	0/0/10590	0/1/3415	0/0/9343	0/0/195	0/0/178	0/1/396	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	1	probably damaging	0.01	DAMAGING	2.82	0	2	missense	nonsynonymous//	0.0004243
exm477849	rs143064419	*FSTL4*	Missense_G580V	chr5:132537712	3/8090	0/21803	0.01983	A	C	0/3/8090	0/0/21803	0/0/3583	0/0/10584	0/3/3409	0/0/9339	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.964	probably damaging	0.03	DAMAGING	2.7	0	2	missense	nonsynonymous//	0
exm1006054	rs116055718	*KRT73*	Missense_V243M	chr12:53008455	3/8097	0/21818	0.01984	A	G	0/3/8097	0/0/21818	0/0/3584	0/0/10590	0/3/3415	0/0/9348	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.772	possibly damaging	0.01	DAMAGING	3.02	0	NA	missense	nonsynonymous//	1.54E-05
exm1083572	rs79276613	*OR4K5*	Missense_N65K	chr14:20388960	3/8097	0/21820	0.01984	A	C	0/3/8097	0/0/21820	0/0/3584	0/0/10590	0/2/3416	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING	2.83	0	2	missense	nonsynonymous//	3.00E-05
exm127544	rs199933063	*TOR1AIP1*	Missense_E121K	chr1:179851998	3/8097	0/21819	0.01984	A	G	0/3/8097	0/0/21819	0/3/3581	0/0/10590	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING *Warning! Low confidence.	3.39	0	NA	missense	nonsynonymous//	0.0007384
exm1362169	rs201536028	*ENGASE*	Missense_E237K	chr17:77076432	3/8097	0/21820	0.01984	A	G	02/01/8097	0/0/21820	0/1/3583	0/0/10590	0/0/3418	0/0/9350	0/0/195	0/0/178	2/0/395	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING	2.57	0	2	missense	nonsynonymous//	n/a
exm1542518	rs201841566	*L3MBTL1*	Missense_Y386F	chr20:42161555	3/8097	0/21817	0.01984	T	A	0/3/8097	0/0/21817	0/1/3583	0/0/10590	0/0/3418	0/0/9347	0/0/195	0/0/178	0/0/397	0/0/376	0/2/257	0/0/273	0/0/247	0/0/1053	0.967	probably damaging	0.04	DAMAGING	2.55	0	2	missense	nonsynonymous//	n/a
exm1552938	rs16981999	*APCDD1L*	Missense_R261C	chr20:57036571	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/0/3584	0/0/10590	0/1/3417	0/0/9350	0/0/195	0/0/178	0/1/396	0/0/376	0/0/259	0/0/273	0/1/246	0/0/1053	0.999	probably damaging	0	DAMAGING	2.88	0	2	missense	nonsynonymous//	0.0002678
exm157841	rs138064546	*PGBD5*	Missense_P522L	chr1:230459181	3/8097	0/21818	0.01984	A	G	3/0/8097	0/0/21818	3/0/3581	0/0/10589	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.997	probably damaging	0	DAMAGING	3.03	0	2	missense	nonsynonymous//	3.02E-05
exm2219293	rs186432117	*SYT12*	Missense_L368F	chr11:66816064	3/8097	0/21819	0.01984	A	G	3/0/8097	0/0/21819	0/0/3584	0/0/10590	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	3/0/256	0/0/273	0/0/247	0/0/1053	1	probably damaging	0.01	DAMAGING	2.52	0	2	missense	nonsynonymous//	
exm240087	rs137983840	*LRP2*	Missense_A3344T	chr2:170038097	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/2/3582	0/0/10590	0/1/3417	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.996	probably damaging	0.04	DAMAGING	2.23	0	2	missense	nonsynonymous//	0.0001049
exm303176	rs200679198	*ZNF619*	Missense_G464R	chr3:40529271	3/8097	0/21819	0.01984	A	G	0/3/8097	0/0/21819	0/3/3581	0/0/10590	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING	2.59	0	2	missense	nonsynonymous//	6.00E-05
exm391978	rs149977507	*KCNIP4*	Missense_R216H	chr4:20731736	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/1/3583	0/0/10590	0/1/3417	0/0/9350	0/1/194	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.634	possibly damaging	0.04	DAMAGING	3	0	NA	missense	nonsynonymous//	
exm417917	rs141061981	*LEF1*	Missense_E71Q	chr4:109088713	3/8097	0/21820	0.01984	G	C	0/3/8097	0/0/21820	0/3/3581	0/0/10590	0/0/3418	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.876	possibly damaging	0.02	DAMAGING *Warning! Low confidence.	3.27	0	NA	missense	nonsynonymous//	1.50E-05
exm43432	rs145749755	*ZMYM6*	Missense_Y106C	chr1:35485065	3/8097	0/21820	0.01984	G	A	0/3/8097	0/0/21820	0/3/3581	0/0/10590	0/0/3418	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.999	probably damaging	0	DAMAGING	2.74	0	2	missense	nonsynonymous//	0.0002847
exm46136	rs182482113	*RSPO1*	Missense_R220W	chr1:38078561	3/8097	0/21817	0.01984	A	G	0/3/8097	0/0/21817	0/0/3584	0/0/10590	0/2/3416	0/0/9347	0/0/195	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	0.993	probably damaging	0	DAMAGING	2.92	0	2	missense	nonsynonymous//	6.00E-05
exm652229	rs75961395	*CFTR*	Missense_G85E	chr7:117149177	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/1/3583	0/0/10590	0/0/3418	0/0/9350	0/1/194	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	0.995	probably damaging	0.01	DAMAGING	2.47	3	2	missense	nonsynonymous//	0.00012
exm652595	rs199687888	*CTTNBP2*	Missense_R948Q	chr7:117407166	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/0/3584	0/0/10590	0/0/3418	0/0/9350	0/2/193	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	1	probably damaging	0.01	DAMAGING	2.92	0	2	missense	nonsynonymous//	0
exm726831	rs113705108	*MROH6*	Missense_R377P	chr8:144652149	3/8097	0/21820	0.01984	G	C	0/3/8097	0/0/21820	0/0/3584	0/0/10590	0/1/3417	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/2/257	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING	1.71	0	2	missense	nonsynonymous//	
exm755882	rs114234833	*PCSK5*	Missense_S1458F	chr9:78943039	3/8097	0/21816	0.01984	A	G	0/3/8097	0/0/21816	0/0/3584	0/0/10590	0/0/3418	0/0/9346	0/2/193	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	0.886	possibly damaging	0.05	DAMAGING	1.74	0	NA	missense	nonsynonymous//	0.0003338
exm772157	rs201244484	*KIAA0368*	Missense_R708C	chr9:114180258	3/8097	0/21819	0.01984	A	G	0/3/8097	0/0/21819	0/2/3582	0/0/10590	0/1/3417	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.999	probably damaging	0.01	DAMAGING	2.12	0	2	missense	nonsynonymous//	2.54E-05
exm864262	rs144737013	*C10orf90*	Missense_F483S	chr10:128153351	3/8097	0/21820	0.01984	G	A	0/3/8097	0/0/21820	0/1/3583	0/0/10590	0/0/3418	0/0/9350	0/0/195	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/1/246	0/0/1053	0.606	possibly damaging	0.04	DAMAGING	2.89	0	NA	missense	nonsynonymous//	0.0002847
exm881231	rs200807047	*OR51E1*	Missense_R125C	chr11:4674129	3/8097	0/21820	0.01984	A	G	0/3/8097	0/0/21820	0/2/3582	0/0/10590	0/0/3418	0/0/9350	0/1/194	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	1	probably damaging	0	DAMAGING	2.78	0	2	missense	nonsynonymous//	0.0001363
exm896540	rs200601314	*NELL1*	Missense_R415C	chr11:20968969	3/8097	0/21819	0.01984	A	G	0/3/8097	0/0/21819	0/1/3583	0/0/10590	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/2/257	0/0/273	0/0/247	0/0/1053	0.64	possibly damaging	0.01	DAMAGING	2.2	0	NA	missense	nonsynonymous//	
exm907999	rs145838163	*OR5D14*	Missense_H254R	chr11:55563792	3/8097	0/21819	0.01984	G	A	0/3/8097	0/0/21819	0/0/3584	0/0/10590	0/3/3415	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.969	probably damaging	0	DAMAGING	2.78	0	2	missense	nonsynonymous//	0
exm937175	rs115978536	*SHANK2*	Missense_P2L	chr11:70858368	3/8097	0/21819	0.01984	A	G	0/3/8097	0/0/21819	0/0/3584	0/0/10590	0/0/3418	0/0/9349	0/2/193	0/0/178	0/0/397	0/0/376	0/1/258	0/0/273	0/0/247	0/0/1053	1	probably damaging	0.01	DAMAGING	3.02	0	2	missense	nonsynonymous//	0
exm1042718	rs201734893	*GCN1L1*	Missense_R2107H	chr12:120575778	3/8095	0/21808	0.01985	A	G	0/3/8095	0/0/21808	0/1/3583	0/0/10590	0/0/3416	0/0/9338	0/2/193	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.996	probably damaging	0.01	DAMAGING	2.14	0	2	missense	nonsynonymous//	0.0005024
exm1207590	rs147234069	*CCNF*	Missense_R239Q	chr16:2489766	3/8097	0/21812	0.01985	A	G	0/3/8097	0/0/21812	0/0/3584	0/0/10590	0/3/3415	0/0/9342	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.997	probably damaging	0.03	DAMAGING	2.86	0	2	missense	nonsynonymous//	3.04E-05
exm1559083	rs146772563	*PTK6*	Missense_G321R	chr20:62162152	3/8097	0/21812	0.01985	A	G	02/01/8097	0/0/21812	0/0/3584	0/0/10590	0/0/3418	0/0/9342	0/1/194	0/0/178	0/0/397	0/0/376	2/0/257	0/0/273	0/0/247	0/0/1053	0.999	probably damaging	0	DAMAGING	3.25	0	2	missense	nonsynonymous//	1.51E-05
exm858712	rs62641727	*C10orf82*	Missense_T74M	chr10:118425172	3/8097	0/21815	0.01985	A	G	0/3/8097	0/0/21815	0/1/3583	0/0/10590	0/0/3418	0/0/9345	0/0/195	0/0/178	0/0/397	0/0/376	0/2/257	0/0/273	0/0/247	0/0/1053	0.879	possibly damaging	0.03	DAMAGING	2.82	0	NA	missense	nonsynonymous//	0.000105
exm865091	rs148481888	*MKI67*	Missense_R2189C	chr10:129902459	3/8097	0/21809	0.01986	A	G	0/3/8097	0/0/21809	0/0/3584	0/0/10590	0/0/3418	0/0/9339	0/0/195	0/0/178	0/0/397	0/0/376	0/2/257	0/0/273	0/1/246	0/0/1053	1	probably damaging	0.05	DAMAGING	1.4	0	2	missense	nonsynonymous//	1.50E-05
(2) Candidate recessive high-penetrance CRC alleles.																																	
Stop mutations																																	
exm1204998	rs150766139	*NTHL1*	Nonsense_Q90X	chr16:2096239	3/8097	0/21820	0.01984	A	G	3/32/8065	0/57/21763	0/18/3566	0/34/10556	0/9/3409	0/13/9337	0/2/193	0/1/177	3/1/393	0/6/370	0/2/257	0/2/271	0/0/247	0/1/1052	NA		N/A	N/A	N/A	0	NA	stop-gained	stop//	0.002304
Missense mutations																																	
exm252852	rs61756360	*PMS1*	Missense_T75I	chr2:190660586	4/8096	0/21817	0.00537	A	G	4/47/8049	0/93/21724	1/16/3567	0/46/10544	3/26/3389	0/45/9302	0/1/194	0/0/178	0/0/397	0/0/376	0/4/255	0/1/272	0/0/247	0/1/1052	1	probably damaging	0	DAMAGING	3.19	0	2	missense	nonsynonymous//	0.0008096
exm970236	rs78900720	*PRDM10*	Missense_T59S	chr11:129827700	4/8096	0/21814	0.00537	A	T	4/31/8065	0/42/21772	0/9/3575	0/11/10579	04/11/3403	0/23/9321	0/9/186	0/1/177	0/0/397	0/0/376	0/2/257	0/5/268	0/0/247	0/2/1051	0.997	probably damaging	0.01	DAMAGING *Warning! Low confidence.	3.97	0	NA	missense	nonsynonymous//	0.001472
exm1549703	rs116905185	*FAM65C*	Missense_D318G	chr20:49221303	3/8097	0/21820	0.01984	G	A	3/182/7915	0/440/21380	1/79/3504	0/232/10358	1/79/3338	0/183/9167	0/4/191	0/3/175	1/12/384	0/7/369	0/4/255	0/4/269	0/4/243	0/11/1042	0.999	probably damaging	0.02	DAMAGING	2.34	0	2	missense	nonsynonymous//	0.006 (3)
exm157841	rs138064546	*PGBD5*	Missense_P522L	chr1:230459181	3/8097	0/21818	0.01984	A	G	3/0/8097	0/0/21818	3/0/3581	0/0/10589	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.997	probably damaging	0	DAMAGING	3.03	0	2	missense	nonsynonymous//	3.02E-05
exm2219293	rs186432117	*SYT12*	Missense_L368F	chr11:66816064	3/8097	0/21819	0.01984	A	G	3/0/8097	0/0/21819	0/0/3584	0/0/10590	0/0/3418	0/0/9349	0/0/195	0/0/178	0/0/397	0/0/376	3/0/256	0/0/273	0/0/247	0/0/1053	1	probably damaging	0.01	DAMAGING	2.52	0	2	missense	nonsynonymous//	
exm270161	rs140297559	*SLC4A3*	Missense_R917C	chr2:220502516	3/8097	0/21819	0.01984	A	G	03/01/8096	0/3/21816	2/0/3582	0/1/10589	0/1/3417	0/2/9347	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	1/0/246	0/0/1053	0.998	probably damaging	0	DAMAGING	2.71	9	2	missense	nonsynonymous//	0.0002706
exm700363	rs200978094	*PXDNL*	Missense_R1181I	chr8:52320642	3/8097	0/21820	0.01984	A	C	3/0/8097	0/1/21819	1/0/3583	0/0/10590	0/0/3418	0/1/9349	0/0/195	0/0/178	0/0/397	0/0/376	2/0/257	0/0/273	0/0/247	0/0/1053	0.927	possibly damaging	0.02	DAMAGING	2.61	0	NA	missense	nonsynonymous//	8.14E-05
exm297309	rs201860756	*TRIM71*	Missense_G597S	chr3:32932485	3/8097	0/21813	0.01985	A	G	3/0/8097	0/2/21811	1/0/3583	0/1/10589	0/0/3418	0/1/9342	2/0/193	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.969	probably damaging	0.05	DAMAGING	1.51	0	2	missense	nonsynonymous//	0.0001505

Dominant alleles (1) were filtered from the entire variant set as follows: predicted not to be benign/tolerated by both SIFT and PP2 or nonsense variants ; excluded probable miscalled SNPs through visual inspection of genotyping clusters; absent in controls to ensure inclusion of potentially high penetrance risk alleles. Recessive alleles (2) were filtered from the entire variant set as follows: predicted not benign or tolerated by both SIFT and PP2; excluded probable miscalled SNPs through visual inspection of genotyping; homozygotes absent in controls to ensure inclusion of potentially high penetrance risk alleles; minor allele frequency =< 0.02 in controls.

* *Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [July 2015 accessed].*

Supplementary Table 19. Homozygous rare damaging allele variants in base-excision and mismatch repair pathways.

SNP	rs_number	Gene	CHR	Effect allele	Reference allele	AFF (homozygous effect allele genotype/heterozygous + reference allele homozygous genotypes)	UNAFF (homozygous effect allele genotype/heterozygous + reference allele homozygous genotypes)	P (Fisher exact test)	GENO.cases	ENO.contro	NGLAND.cas	GLAND.cont	cotland.cas	otland.contr	RTUGAL.ca	TUGAL.cont	OLLAND.cas	LLAND.cont	SPAIN.cases	PAIN.contro	RMANY.cas	MANY.cont	ExAC freq (EUR,non-Finnish)*	ExAC number of homozygous alleles /alllele number ((EUR,non-Finnish)*
Base excision repair pathway (GO:0006284)																								
exm1204998	rs150766139	*NTHL1*	16	A	G	== 3/8097	== 0/21820	0.01984	3/32/8065	0/57/21763	0/18/3566	0/34/10556	0/9/3409	0/13/9337	0/2/193	0/1/177	3/1/393	0/6/370	0/2/257	0/2/271	0/0/247	0/1/1052	0.002304	0/65960
exm54989	rs36053993	*MUTYH*	1	A	G	== 4/8096	== 1/21819	0.02103	4/132/7964	1/277/2154	3/56/3525	0/107/1048	1/57/3360	1/148/9201	0/7/188	0/5/173	0/5/392	0/1/375	0/6/253	0/10/263	0/1/246	0/6/1047	0.003958	2/65440
exm1204981	rs1805378	*NTHL1*	16	G	A	== 1/7840	== 0/21547	0.2668	1/28/7812	0/50/21497	1/15/3568	0/28/10562	0/11/3407	0/16/9334	0/2/193	0/1/177	0/0/397	0/1/375	NA	NA	0/0/247	0/4/1049	0.003004	1/64586
exm288235	rs104893751	*OGG1*	3	A	G	== 1/8099	== 0/21819	0.2707	8022/77/1	21617/202/	3550/33/1	10495/95/0	3390/28/0	9256/93/0	194/1/0	175/3/0	390/7/0	368/8/0	254/5/0	272/1/0	244/3/0	1051/2/0	0.003229	0/66270
exm288284	rs113561019	*OGG1*	3	A	G	== 1/8099	== 0/21818	0.2707	8016/83/1	21576/242/	3544/39/1	10477/113/	3390/28/0	9251/98/0	191/4/0	172/6/0	391/6/0	370/5/0	256/3/0	268/5/0	244/3/0	1038/15/0	0.006295	3/66718
exm1204957	rs146347092	*NTHL1*	16	A	G	== 1/8099	== 0/21814	0.2708	########	0/33/21781	0/2/3582	0/7/10583	########	0/26/9318	0/0/195	0/0/178	0/0/397	0/0/376	0/0/259	0/0/273	0/0/247	0/0/1053	0.0001856	0/64642
exm824096	rs142580756	*ERCC6*	10	A	G	== 1/8098	== 0/21814	0.2708	########	0/26/21788	########	0/12/10573	0/1/3416	0/12/9337	0/0/195	0/0/178	0/1/396	0/2/374	0/0/259	0/0/273	0/0/247	0/0/1053	0.001171	0/66612
exm698694	rs147215490	*POLB*	8	G	A	== 1/8082	== 0/21736	0.2711	########	0/7/21729	0/0/3581	0/0/10577	########	0/2/9288	0/0/195	0/0/178	0/0/397	0/1/371	0/0/259	0/0/273	0/2/244	0/4/1042	0.002223	2/66576
exm694461	rs78488552	*WRN*	8	C	G	== 1/8099	== 1/21809	0.4683	8002/97/1	21528/281/	3533/51/0	10435/154/	3383/35/0	9237/103/0	192/3/0	176/2/0	394/2/1	368/8/0	256/3/0	270/3/0	244/3/0	1042/11/0	0.00468	3/66666
exm891143	rs34511735	*USP47*	11	G	C	== 2/8098	== 5/21806	1	2/309/7789	5/815/2099	0/119/3465	3/378/1020	2/156/3260	2/371/8969	0/6/189	0/7/171	0/12/385	0/15/361	0/8/251	0/10/263	0/8/239	0/34/1019	0.01807	12/66508
Mismatch repair pathway (GO:0006298)																								
exm252852	rs61756360	*PMS1*	2	A	G	== 4/8096	== 0/21817	0.005371	4/47/8049	0/93/21724	1/16/3567	0/46/10544	3/26/3389	0/45/9302	0/1/194	0/0/178	0/0/397	0/0/376	0/4/255	0/1/272	0/0/247	0/1/1052	0.0008096	0/66700
exm54989	rs36053993	*MUTYH*	1	A	G	== 4/8096	== 1/21819	0.02103	4/132/7964	1/277/2154	3/56/3525	0/107/1048	1/57/3360	1/148/9201	0/7/188	0/5/173	0/5/392	0/1/375	0/6/253	0/10/263	0/1/246	0/6/1047	0.003958	2/65440
exm603891	rs200513014	*PMS2*	7	G	A	== 1/8099	== 0/21818	0.2707	########	0/15/21803	########	0/4/10586	0/2/3416	0/9/9339	0/0/195	0/0/178	0/0/397	0/1/375	0/1/258	0/0/273	0/0/247	0/1/1052	0.0004118	0/65558
exm69401	rs5745459	*MSH4*	1	G	A	== 2/8098	== 4/21812	0.665	2/183/7915	4/463/2134	1/78/3505	2/237/1035	1/85/3332	2/202/9142	0/3/192	0/0/178	0/11/386	0/9/367	0/1/258	0/1/272	0/5/242	0/14/1039	0.0123	2/65446

* *Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [July 2015 accessed].*

Supplementary Table 20. Candidate compound heterozygous high-penetrance CRC alleles

Gene	***Number of compound heterozygous cases/gene***	**SNP**	**rsID**	**Position**	**A1**	**A2**	**Count.cases**	**Count.controls**	**Mutation**	**EAF (cases/controls)**	**ExAC freq (EUR,non-Finnish)***
NOTCH2	2	exm89497	rs35586704	chr1:120458122	A	T	0/78/8022	0/203/21609	Missense_L2408H	0.004815/0.004653	0.002579
		exm89650	rs147223770	chr1:120478125	C	A	0/49/8051	0/117/21703	Missense_F1209V	0.003025/0.002681	0.004586
DNAJC17	2	exm1149787	rs140603715	chr15:41060221	G	A	0/53/8044	0/145/21671	Missense_M278V	0.003273/0.003323	0.002193
		exm1149789	rs186113485	chr15:41062758	A	G	0/4/8093	0/12/21803	Missense_R22Q	0.000247/0.000275	0.0005519

probable miscalled SNPs through visual inspection of genotyping clusters, (3) number of rare damaging heterozygotes per gene in controls <<=1, (4) minor allele frequency <=< 0.02 in controls.

EAF=effect allele frequency

** Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [July 2015 accessed].*