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MUCH OF THE POPULATION GENETIC RISK OF COLORECTAL CANCER IS LIKELY TO BE MEDIATED THROUGH SUSCEPTIBILITY TO ADENOMAS

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Abstract

Several single nucleotide polymorphisms (SNPs) have been associated with colorectal cancer (CRC) susceptibility. Most CRCs arise from adenomas, and SNPs might therefore affect predisposition to CRC by increasing adenoma risk. We found that 8 of 18 known CRC-associated SNPs (rs10936599, rs6983267, rs10795668, rs3802842, rs4444235, rs1957636, rs4939827, and rs961253) were over-represented in CRC-free patients with adenomas, compared with controls. Ten other CRC-associated SNPs (rs6691170, rs6687758, rs16892766, rs7136702, rs11169552, rs4779584, rs9929218, rs10411210, rs4813802, and rs4925386) were not significantly associated with adenoma risk. Genetic susceptibility to CRC in the general population is likely to be mediated in part by predisposition to adenomas.

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Authors' contributions: LGC-C, AGZ, JW, DM, MMB and IT planned and designed the study. AMJ, KH and TC carried out sample genotyping. LGC-C, AGZ, JW and IT performed the statistical analyses. DM, RR, AL, AGZ, IT, JW and MMB co-ordinated sample collection and characterisation. IT wrote the manuscript.

Keywords

colorectal adenomas; intermediate phenotype; risk factor; colorectal carcinoma

Many, perhaps most, colorectal carcinomas (CRCs) develop from adenomatous precursors. Some of the known Mendelian CRC syndromes are typified by primary predisposition to adenomas (for example, familial adenomatous polyposis, FAP), whereas others (for example, 1 Lynch syndrome) are characterized by a primary predisposition to carcinomas and there is no striking excess of adenomas¹. Recent studies have identified haplotype-tagging single nucleotide polymorphisms (tagSNPs) at which common alleles are associated with increased CRC risk in the general population²⁻⁸. However, all these studies have focused on patients with CRC, and it is not known whether the functional variants tagged by these SNPs act through increasing the risk of adenomas, carcinomas or both. The familial risk of colorectal adenomas is estimated as similar to that of CRCs⁹, suggesting that some of the common genetic predisposition to CRC may be mediated through increased adenoma risk. Indeed, adenomas can be regarded as an intermediate phenotype between SNP and cancer¹⁰, and under some plausible scenarios, CRC predisposition polymorphisms might be more strongly associated with the risk of colorectal adenoma(s) than with CRC. An adenoma predisposition SNP might affect adenoma development only, or might also have an effect at the malignant stage of tumorigenesis, or both, and it is not practical to distinguish between these possibilities¹¹. However, a SNP allele should not be over-represented in adenoma-only cases if it affects growth solely at the carcinoma stage of tumorigenesis.

Here, we tested the hypothesis that common CRC polymorphisms increase susceptibility to adenomas. Adenoma cases (N=1,755) were derived from the APC¹² and APPROVe¹³ adenoma chemoprevention trials, and from the genetics clinic-based UK (CORGI) study⁷ (Tables 1 and 2, Supplementary Methods). The recruitment from these studies led to an enrichment for early-onset, multiple or advanced adenomas compared with the general population, and we reasoned that this would enhance our power to detect associations between SNP alleles and adenoma risk. For all studies, we excluded any cases who reported a personal or family history of colorectal cancer. Controls (N=3,976) were from population-based collections (CGEMS¹⁴ and CCFR¹⁵), or were spouses/partners of cases and selected for no history of colorectal disease (UK). All individuals were of white, Northern European ancestry, as determined from principal component analysis (part of APC, CGEMS, CCFR) or from self-reported data (remainder of APC, APPROVe, UK). No case or control had previously been used for the identification in GWAS of the CRC predisposition SNPs analysed (Table 2). We genotyped 18 CRC predisposition SNPs in all samples (Table 2). Overall, there was evidence from the directions of effect that the CRC predisposition alleles at the 18 SNPs were also associated with adenoma risk (15/18 concordant between adenoma and CRC, $P=0.0075$, sign test). We then analysed associations at individual SNPs. Using a false discovery rate threshold of $q=0.05$ to denote significance, we found that eight of the SNPs (rs10936599, rs6983267, rs10795668, rs3802842, rs4444235, rs1957636, rs4939827, rs961253) were associated with adenoma risk, without evidence of inter-study heterogeneity. In all eight cases, the risk allele was the same as that for CRC, and some associations (rs6983267, rs3802842, rs4939827, rs961253) were very strong (Table 2). We found no convincing evidence that the remaining ten SNPs (rs6691170, rs6687758, rs16892766, rs7136702, rs11169552, rs4779584, rs9929218, rs10411210, rs4813802, rs4925386) were associated with adenoma susceptibility (Table 2). In a case-only analysis stratified by study, we searched for associations between SNP genotypes and the clinico-pathological features shown in Table 1. The only good evidence for such an association was between rs6983267 and adenoma multiplicity (OR=0.76, $P=0.002$), suggesting that rs6983267 has effects on adenoma initiation or early progression.

There is no reason *a priori* to assume that a colorectal cancer predisposition polymorphism should increase the risk of benign lesions such as adenomas. However, we have shown that approaching half of the known CRC predisposition SNPs are formally associated with an increased risk of colorectal adenomas. SNPs associated with adenoma predisposition could, in principle, be sub-divided into those that promote initiation, those that promote progression to “advanced” adenomas, and those that do both. The first type of SNP should be more frequent in those with multiple adenomas and the second, in those with large adenomas, phenotypes that were enriched in all three of our studies. Only one adenoma SNP showed any such association in a cases-only analysis; this was rs6983267, at which the risk allele was associated with multiple adenomas, suggesting an effect on initiation. There was no evidence that any other SNP acted differentially on adenoma initiation and progression. Our study had about 70% power to detect a “typical” association between a SNP allele and adenoma risk (see Supplementary Methods), but power was likely to be lower for some SNPs (for example, with lower allele frequencies or risks). We cannot, therefore, exclude the possibility that some CRC SNPs additional to the eight detected had effects on adenoma risk. However, for some CRC SNPs, such as rs6691170 and rs6687758 (Table 2), we found very little evidence indeed of an association with adenoma risk, and we suggest that these SNPs may have their effects on the malignant stage of colorectal tumorigenesis.

Our study principally relied on adenoma cases collected as part of clinical trials and for whom directly matched controls were not available. We therefore utilised controls with publicly-available genotype data. These controls were relatively numerous and this provided our study with good statistical power, despite the fact that the controls were population-based and not known to be adenoma-free (see Supplementary Methods). We matched cases and controls by ethnicity to the fullest possible extent. Whilst this is common practice in genetic association studies, there can remain the potential for both small genetic differences and environmental differences between cases and controls. Furthermore, it is possible that under-reporting of a family history of CRC by trial participants led us to detect some false associations, although the chance of this factor explaining the strong associations at rs6983267, rs3802842, rs4939827 and rs961253 is very low (estimated $P < 0.01$).

In summary, we have shown that much of the genetic risk of CRC in the general population is likely to be mediated through differential adenoma risk. In principle, especially if further studies can assign SNPs as adenoma-predisposing, carcinoma-predisposing or both, such variation could be used to modulate population-based CRC-prevention measures, in a way analogous to the different methods of prophylaxis used for FAP and Lynch syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Cancer Family Registry (UO1 CA074794), and The University of Hawaii Colorectal Cancer Family Registry (UO1 CA074806).

Abbreviations

SNP	Single nucleotide polymorphism
CRC	Colorectal cancer
APC	Adenoma Prevention with Celecoxib study
Corgi	Colorectal gene identification study
APPROVe	Adenomatous Polyp PREvention On Vioxx study
FAP	Familial adenomatous polyposis
CGEMS	Cancer Genetic Marker of Susceptibility study
CCFR	Colon Cancer Family Registry

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Table 1
Summary of the numbers and clinico-pathological features of individuals in the study

Note that, for some patients, full details were not frequently collected at routine histological assessment (for example, adenoma size and location were often not present on histology reports in the UK patients). In addition to the main genetic susceptibility (case-control) analysis, each of the variables in the Table was tested for association with SNP genotypes in a case-only analysis. “Advanced adenoma” was defined as ≥1cm diameter, and/or villous/tubulovillous histology, and/or severe dysplasia.

	APC/CGEMS	APPROVe/CCFR	UK
No. cases	1155	436	164
No. controls	2367	999	310
Male	2376	1514	
Female	1146	1423	
Mean age at first adenoma	60	58	56
No. aged <60	596	251	57
No. aged ≥60	518	185	49
No. with adenoma ≥1cm	474	133	-
No. with no adenoma ≥1cm	640	303	-
Mean no. adenomas	2.1	1.7	2.1
No. with ≥3 adenomas	294	64	-
No. with <3 adenomas	822	372	-
No. with advanced adenoma	548	169	-
No. without advanced adenoma	569	267	-
No. with left- sided adenoma(s) only	359	193	-
No. with right- sided adenoma(s) only	459	165	-

Table 2
Association statistics at each of the 18 SNPs tested for effects on adenoma risk

SNP – CRC tagSNP ID

Location – chromosome: position (bases)

Gene – closest coding transcript, not necessarily the target of the functional variation

OR_{meta} – odds ratio from STATA *metan* analysis of allele counts in the 3 data sets under a fixed effects model (italic/underlined denotes direction of effect opposite from CRC risk)

L, U 95% CI – lower and upper 95% confidence intervals for OR_{meta}

P_{meta} fixed (1) – one-tailed meta-analysis P (bold denotes significant at P=0.02, FDR q=0.05)

P_{meta} fixed (2) – two-tailed equivalent of P_{meta} fixed (1)

Full results are shown in Supplementary Data.

SNP	Location	Gene	OR _{meta}	L 95%CI	U 95%CI	P _{meta} fixed (1)	P _{meta} fixed (2)
rs6691170	1:220,112,069	DUSP10	<u>0.923</u>	0.851	1.000	0.975	0.051
rs6687758	1:220,231,571	DUSP10	<u>0.911</u>	0.827	1.005	0.969	0.062
rs10936599	3:170,974,795	TERC	0.888	0.809	0.975	0.007	0.013
rs16892766	8:117,699,864	EIF3H	<u>0.966</u>	0.839	1.111	0.813	0.626
rs6983267	8:128,482,487	MYC	0.832	0.769	0.901	2.68×10⁻⁶	5.36×10 ⁻⁶
rs10795668	10:8,741,225	None	0.884	0.809	0.966	0.004	0.007
rs3802842	11:110,676,919	POU2AF1	1.223	1.124	1.133	1.74×10⁻⁶	3.48×10 ⁻⁶
rs7136702	12:49,166,483	DIP2B	1.080	0.995	1.173	0.033	0.066
rs11169552	12:49,441,930	DIP2B	0.953	0.873	1.041	0.143	0.285
rs4444235	14:53,480,669	BMP4	1.147	1.061	1.240	0.001	0.001
rs1957636	14:53,629,768	BMP4	1.104	1.013	1.203	0.012	0.024
rs4779584	15:30,782,048	GREM1	1.067	0.969	1.175	0.093	0.185
rs9929218	16:67,378,447	CDH1	0.969	0.888	1.058	0.242	0.484
rs4939827	18:44,707,461	SMAD7	0.843	0.778	0.912	1.17×10⁻⁵	2.34×10 ⁻⁵
rs10411210	19:38,224,140	RHPN2	0.961	0.845	1.093	0.272	0.544
rs961253	20:6,352,281	BMP2	1.177	1.085	1.277	4.42×10⁻⁵	8.85×10 ⁻⁵
rs4813802	20:6,647,595	BMP2	1.061	0.973	1.157	0.091	0.181
rs4925386	20:60,354,439	LAMA5	0.922	0.847	1.004	0.032	0.063