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Investigation of the effects of DNA repair gene polymorphisms on the risk of colorectal cancer

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Abstract

Despite their prime candidate status, polymorphisms near genes involved in DNA repair or in other functions related to genome stability have been conspicuously under-represented in the significant associations reported from genome-wide association studies (GWAS) of cancer susceptibility. In this study, we assessed a set of single-nucleotide polymorphisms (SNPs) near 157 DNA repair genes in three colorectal cancer (CRC) GWAS. Although no individual SNP showed evidence of association, the set of SNPs as a whole was associated with colorectal cancer risk. When candidate SNPs were examined, our data did not support most of the previously reported associations with CRC susceptibility, an exception being an effect of the MLH1 promoter SNP –93G>A (rs1800734). Rare variants in *CHEK2* (I157T and possibly del1100C) also appear to be associated with CRC risk. Overall, the absence to date of disease-associated DNA repair SNPs in cancer GWAS may be explained by a combination of the following: (i) many loci with individually very small effects on risk; (ii) rare alleles of moderate effect and (iii) subgroups of CRC, such as those with microsatellite instability, associated with specific variants. It will be particularly intriguing to determine whether any GWAS across cancer types identify DNA variants that predispose to cancers of more than one site.

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Supplementary data

Supplementary Table 1 is available at *Mutagenesis* Online.

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Introduction

Colorectal cancer genetics

Colorectal carcinoma (CRC) affects 5–6% of the Western world population during their lifetime, with a small male preponderance. In Europe, CRC causes more deaths than any other cancer in the absence of a major avoidable risk factor such as smoking. Although environmental factors, such as diet, influence CRC risk, specific agents and mechanisms of action have been difficult to pin down. Inherited factors also play an important role in CRC predisposition, with a family history of the disease probably being the strongest, easily quantifiable risk factor (apart from a previous personal history of colorectal tumours). Most CRCs probably develop from benign lesions, mainly adenomatous polyps. Screening for adenomas and subsequent removal by colonoscopy or sigmoidoscopy can reduce CRC risk. Many Western countries now have population screening programmes based on these techniques or faecal occult blood testing. Thus, while it is expected that deaths from CRC will fall in Europe as population screening becomes more effective, CRC will continue to be a major killer and the public health burden of colorectal screening is likely to increase considerably.

The risks of many common diseases, including cancers, are known to depend on inherited factors. Recent progress has led to the identification of panels of common genetic variants that influence risk. For CRC, the known predisposition genes are of two types. Firstly, there patients who harbour high-penetrance mutations that cause rare Mendelian syndromes, often in the familial setting; these include CRC syndromes such as familial adenomatous polyposis (FAP), Lynch syndrome, MUTYH-associated polyposis (MAP) and juvenile polyposis (JPS). Secondly, individuals may carry common genetic variants associated with modest increases in CRC risk in the general population.

The identification of common polymorphisms associated with CRC risk has occurred in two phases. Initially, such studies were confined to the analysis of candidate polymorphisms, but studies were small and, in retrospect, probably under-powered. It is debatable whether any of the reported associations were demonstrated to sufficiently stringent levels of evidence to be regarded as ‘proven’ (1,2). However, more recently, a genome-wide hypothesis-free approach has been employed in which haplotype tagging single-nucleotide polymorphisms (tagSNPs) are used to screen for associations based on linkage disequilibrum (LD) mapping. For CRC, such genome-wide association studies (GWAS) have identified 17 tagSNPs associated with CRC risk modulation at stringent levels of significance ($P < 5 \times 10^{-8}$) (3–6). The studies have involved Discovery Phases based on hundreds of thousands of tagSNPs typed in a total of ~10 000 CRC cases and controls, and multiple Validation Phases involving tens of thousands of cases and controls derived from the UK and COGENT collaborators throughout Europe (5,7).

Functions of CRC-associated single-nucleotide polymorphisms

The nature of the functional variation that is correlated with these single-nucleotide polymorphisms (SNPs) is largely unknown, and studies to identify such variation can be difficult and time-consuming. For one of the CRC tagSNPs, rs6983267, there is evidence

that it itself is functional (8). It lies a few hundred kilobases upstream of the c-Myc oncogene and changes a TCF4-binding site. The region around the SNP is capable of driving reporter gene expression in the same locations as endogenous Myc. A further CRC tagSNP, rs4779584, near Gremlin1 is an example of a synthetic association. Its association with CRC risk actually results from two independent functional variants tagged by rs16969681 and rs11632715. rs16969681 may in fact be functional (4).

Overall, GWAS in CRC have provided excellent evidence of the important molecular pathways that influence disease risk in the general population. Of the 17 SNPs above, 7 are adjacent to genes (Gremlin1, BMP2/4, SMAD7) that act in the bone morphogenetic protein (BMP) pathway. Although in theory the tagSNPs identified may act on other genes in *cis* or in *trans*, the probability of so many being near BMP genes is ~10^{-9}. Moreover, two other SNPs are near genes (Laminin A5 and DIP2B) for which there is evidence for interaction with the BMP pathway.

A further CRC tagSNP, rs10936599, lies within an intron of the myoneurin gene (9). However, the region is gene-rich and SNPs in very strong LD with rs10936599 lie very close to three or four other genes. The strongest candidate gene near rs10936599 is the telomerase RNA component (*TERC*), which encodes the RNA template on which telomerase reverse transcriptase acts to maintain chromosome ends. Detailed analyses have shown that the risk allele at rs10936599 is in perfect LD with an SNP within the *TERC* transcript. This allele is associated not only with CRC risk but also with longer telomeres in both peripheral blood and normal colorectal mucosa. Longer chromosome telomeres are, other things being equal, predicted to reduce cellular senescence and apoptosis. As is the case for the BMP pathway SNPs, *TERC* variation increases the risk of colorectal adenomas as well as CRCs, indicating an effect at early stages of tumorigenesis. Epidemiological evidence regarding associations between telomere length and CRC risk has been mixed, but the genetic findings have provided excellent evidence in favour of long telomeres being associated with disease.

DNA repair and CRC risk

Carcinogenesis generally depends on the acquisition of somatic mutations by a susceptible cell. On this basis, it is to be expected that individuals with profound defects in DNA repair will be at greatly increased risk of cancer and other malignancies. Many examples of patients with rare, but highly penetrant, germ line mutations in the major DNA repair pathways do indeed exist and almost all these patients have an increased risk of cancer. Mutations in genes involved in maintaining genome integrity, through processes such as normal chromosome segregation, also increase the risk of cancer. For reasons that remain partly obscure, different types of DNA repair defect predispose to different cancer spectra. Colorectal cancer, for example, can be caused by two forms of high-penetrance DNA repair defect: recessive mutations in the DNA glycosylase *MUTYH* which cause defective base excision repair; and dominant mutations in any of the four DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). Some variants in genes such as *MUTYH*, *MSH2* and *MLH1* have been proposed to act as low- or moderate-penetrance susceptibility alleles for CRC, although evidence in their favour is generally mixed (see below).

In fact, DNA repair and genome integrity SNPs—henceforth called 'DNA repair SNPs'—are striking by their absence in the list of common CRC predisposition variants no known DNA repair gene is tagged by the known predisposition SNPs for CRC. This has several potential causes. One highly plausible explanation is that DNA repair and genome integrity are so important to the cell and organism that any alleles with more than very small functional effects are strongly selected against. Such alleles are very unlikely to drift up to polymorphic levels. Nevertheless, common DNA repair alleles with very small effects on cancer risk may still exist, yet their effects are too small—with odds ratios (OR) <1.1 per allele—to be detected individually even in the several thousand samples employed for GWAS. *En masse* (or as a class), however, an effect of DNA repair SNPs on cancer susceptibility might be detectable.

We have therefore analysed our data from three GWAS from the UK to search specifically for effects of DNA repair SNPs on CRC risk.

Methods

Patients were recruited from three GWAS, the ColoRectal tumour Gene Identification (CORGI) study, the Scottish Colorectal Cancer Study (COGS) and the VICTOR/QUASAR2/1958 Birth Cohort data sets (VQ58). These cohorts comprised a total of 3334 CRC (or severe adenoma) cases and 4628 controls; further details are provided in (4). All studies received appropriate local research ethics committee approval.

Methods for genotyping using Illumina Hap550 and Hap300 SNP arrays have been described previously (4). All data had previously been subjected to standard, but rigorous quality control assessment (4) and converted into PLINK binary file format for analysis (http://pngu.mgh.harvard.edu/purcell/plink/).

One hundred and fifty-seven DNA repair genes and other genes involved in maintaining genome integrity were identified from a published list (supplementary Table 1 is available at *Mutagenesis* Online). Each gene from this list had a set of SNPs retrieved using dbSNP126 and HapMap Release 24 Phase II by inputting genomic co-ordinates flanking the coding region of each gene by ±100 kb to cover control regions. SNPs within these regions flanking each gene were identified from the content of the Hap300 and/or Hap550 arrays.

Basic association analysis was performed for each autosomal SNP using the PLINK package. QQ-plots of the chi-squared association statistic were constructed for each cohort and we found $\lambda_{GC} < 1.05$ in all three cases (details not shown). Association tests for individual SNPs were carried out using allelic, Cochran–Armitage and recessive models. Meta-analysis was performed using the Mantel–Haenszel method on all SNPS present in two or all data sets. We reported fixed effects statistics unless there was evidence of heterogeneity among sample sets ($P_{het} < 0.05$ or $I^2 > 75\%$), in which case random effects statistics were reported. For the whole set of SNPs, a simple consistency test between the three data sets was performed based on direction of effect and an expectation that one quarter of SNPs would show the same direction by chance. Set-based tests were also performed on all SNPs and those most strongly associated with CRC in PLINK (http://

pngu.mgh.harvard.edu/~purcell/plink/anal.shtml#set), which calculates a statistic for each set as the mean of these single-SNP statistics, and determines significance using permutation of case–control status. SNPs in LD ($r^2 > 0.2$) were removed from this part of this analysis.

Results

We identified 6216 SNPs within 100 kb of the 157 DNA repair loci that were present on the Illumina Hap550 arrays; ~60% of these SNPs were also present on the Hap370 arrays. Following meta-analysis in the three GWAS series, only one SNP (Table I) showed evidence of association with CRC risk under the allelic, additive or recessive models using a threshold of $P_{meta} = 10^{-4}$ (approximating to a Bonferroni correction at $P = 0.05$). However, this SNP was rs10411210, a known CRC predisposition SNP that lies within an intron of rhophilin2 (*RHPHN2*) but is also within 100 kb of the DNA repair gene *FAAP24*. We have previously presented evidence that favours *RHPHN2* as the target of the functional variation tagged by rs10411210 (11).

Four other independent SNPs were associated with CRC at uncorrected $P = 0.001$ in the additive model (Table I). We attempted *in silico* replication of the association signals at these four SNPs in three further CRC case–control data sets, NSCCG and SOCCS that comprised a total of 9713 individuals from the UK and 1012 from Australia [details in (4)]. However, for all these SNPs, no evidence of replication was found (combined $P_{meta} > 0.01$, meta-analysis of all data sets).

Previously reported associations between DNA repair polymorphisms and CRC risk

Especially in the last 10 years, tens of studies have addressed associations between CRC risk and candidate DNA repair polymorphisms. Many of these studies were reviewed by Naccarati *et al*. (12). Perhaps the best example of a DNA repair SNP being associated with CRC risk is MLH1-93G > A (rs1800734), for which Whiffin *et al*. (13) provided good evidence of association with CRC overall [OR per allele = 1.06, 95% confidence interval (CI) 1.00–1.11, $P = 0.037$] and excellent evidence that this effect was present only in the microsatellite-unstable sub-group (OR per allele = 1.39, 95% CI 1.17–1.64, $P = 1.45 \times 10^{-4}$). Meta-analysis with other smaller studies (13–20) confirmed these findings. Although the samples reported in our study were not all assessed for microsatellite instability, our data supported an effect of rs1800734 on CRC risk (OR per allele = 1.07, 95% CI 0.98–1.15, $P = 0.073$).

The data from other candidate DNA repair gene studies does not generally provide convincing evidence of associations with CRC risk. A small selection of such candidates is shown in Table II (15,17,19–31), together with the results from the best single-SNP tag in our three GWAS. Even allowing for the modest tagging (low pairwise r^2) of some of the candidate SNPs by SNPs on the Hap300/Hap550 arrays, our data provide little or no evidence to support the hypothesis that any of the chosen SNPs is a marker of CRC predisposition (Table II).

In terms of rarer DNA repair polymorphisms that are not well tagged by SNPs on the Hap300/Hap550 arrays, there exist two major candidates: heterozygote *MUTYH* mutants,

principally Tyr179Cys (rs34612342) and Gly396Asp (rs36053993) that have combined allele frequencies of ~1.5% in the UK; and *CHEK2* variants 1100delC and Ile157Thr that have frequencies of ~0.5 and <0.1% in the UK (although the latter is more prevalent in other regions such as the Baltic states). The *MUTYH* state-of-the-art illustrates well the problems of assessing rare, low-penetrance cancer predisposition variants. Even in a study of 20 565 cases and 15 524 controls by Theodoratou *et al*. (32), results were inconclusive, showing a borderline significant association (OR = 1.16, 95% CI: 1.00–1.34, $P = 0.05$). Given that there are some potential sources of bias in CRC cohorts—such as the presence of *MUTYH* homozygotes in the relatives of familial cases—the case for *MUTYH* heterozygotes having raised CRC risk remains unproven.

For *CHEK2* 1100delC, a recent meta-analysis by Xiang *et al*. (33) found a significant ~2-fold increased risk of CRC in carriers (OR = 2.11, 95% CI 1.41–3.16, $P = 0.0003$ for unselected cases). A crude meta-analysis of non-overlapping studies of *CHEK2* I157T and CRC risk (34–38) also found a highly significant association (OR = 1.56, 95% CI 1.32–1.84, $P = 2.6 \times 10^{-7}$, Table III). While the test statistic is not quite at conventionally accepted GWAS levels of significance, this association appears compelling.

Set-based analyses

We examined the direction of OR for the 5609 SNPs successfully genotyped in all GWAS series in order to determine whether there was a tendency for a sub-set of truly disease-associated SNPs to show consistent directions of effect across the three data sets. In 1404 cases, the direction was consistently above or below unity in CORGI COGS and VQ58. This compared with an expectation under a modified sign test of 1402 ($P = 0.98$, Fisher's exact test). Since the sign test might have lacked sensitivity, we also undertook an *en masse* association test for all the DNA repair SNPs as a set of candidate SNPs. After excluding all SNPs in moderate or greater pairwise LD ($r^2 > 0.2$), the overall test statistic was significant ($P = 0.00799$). Thus, there may be an effect of some DNA repair SNPs on CRC risk, yet the effect of any individual SNP is too small to readily be detected in individual SNP analyses in the sample sets used.

Discussion

Candidate gene analyses have failed to provide convincing evidence of DNA repair SNPs that are directly involved in predisposition to colorectal cancer. Here, we have analysed a panel of tagSNPs flanking DNA repair genes and failed to find good evidence that any individual SNP influences the risk of CRC in the general UK population. In general, GWAS of other cancers have failed to find similar associations. In fact, the only cancer susceptibility GWAS that has found variation likely to affect DNA repair is one on breast cancer (SNP rs999737 near *RAD51L1*) (39). We have, however, provided evidence using *en masse* (SNP set) analysis that variation around DNA repair loci does contribute to CRC risk. Clearly, set-based tests must be interpreted cautiously, but the examples of Lynch syndrome and MAP show that DNA repair variants can influence CRC risk. The possibility clearly exists that several DNA repair SNPs have small effects on CRC risk—probably too small to

find easily using GWAS—and furthermore that an individual's overall DNA repair capacity (40) might be associated with CRC susceptibility.

DNA repair capacity, measured by assays such as micronucleus formation and radiosensitivity, has been reported as highly heritable (41–43). Even if these results accurately reflect more general variation in DNA repair, they are not necessarily incompatible with the findings that common cancer susceptibility alleles have only rarely been found near DNA repair genes. Potential non-exclusive explanations for this apparent inconsistency include the following:

- **(i)** heritability results from low variation in intrinsic DAN repair capacity, caused by a small genetic contribution, but even smaller environmental and random contributions;
- **(ii)** polygenic model: many loci with individually very small effects influence DNA repair capacity;
- **(iii)** multiple rare alleles of moderate effect influence DNA repair capacity, these alleles not drifting to high frequencies owing to strong selective constraints;
- **(iv)** sub-groups of CRC, such as those with microsatellite instability, are associated with specific DNA variants, but most studies are not empowered to detect these effects; and
- **(v)** the relevant DNA repair variants are not present on or tagged by commercial SNP array content.

The set test results reported above support (ii) and the *CHEK2* data support (iii). The data in support of an association between MLH1-93G > A and microsatellite-unstable CRC provide evidence for (iv).

GWAS in CRC have not generally discovered variation in pathways that could be described as strong candidates based, for example, on previous studies of individual genes. For example, none of the nine main Mendelian CRC genes has been shown to harbour low-penetrance susceptibility variants to date. CRC GWAS have, however, thrown up a new list of candidate genes, and studies based on those have already been successful. In other cases, unexplained and unexpected associations have been found. For example, while bearing in mind that the genes influenced by functional variation may not be those nearest to the GWAS tagSNP, it seems likely that variation in *EIF3H* (44), an apparently ubiquitously expressed transcription elongation factor, has specific effects on CRC risk; the reasons for this are entirely unclear. Despite these examples, examination of variation in DNA repair genes remains a priority in forthcoming studies to detect and examine rarer cancer predisposition variants through screens based on genome-wide or focussed large-scale sequencing. Analysis of CRC risk in carriers of heterozygous *MUTYH* mutations, where ~1% of the population are at hypothetically increased risk, has shown both the promise and the inherent problems of such rare variant studies. It will also be intriguing to determine whether any large GWAS across cancer types can identify DNA repair variants that predispose to cancers of more than one site.

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Supplementary Material

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Table I

Individual DNA repair tagSNP association statistics

Chr	BP	SNP	*P*	OR	*Q*	I^2	Gene
19	38224140	rs10411210	1.27×10^{-5}	0.6882	0.3106	2.73	*FAAP24*
11	118569768	rs12417928	1.03×10^{-4}	1.378	0.6793	0	*H2AFX*
14	20094459	rs1243647	4.00×10^{-4}	0.8168	0.6255	0	*APEX1*
19	38237541	rs6510337	5.83×10^{-4}	0.8456	0.7768	0	*FAAP24*
19	48854794	rs2239372	7.78×10^{-4}	1.1104	0.4561	0	*XRCC1*
9	32893868	rs1470217	9.28×10^{-4}	1.1212	0.466	0	*APTX*

Chr, chromosome; BP, position in base pairs (dbSNP Build 36); *P*, meta-analysis *P* value; OR, odds ratio per allele relative to the minor allele; *Q*, P_{het}, I^2, % heterogeneity; Gene, DNA repair gene in region of SNP.

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Table II

Associations between CRC susceptibility and Candidate SNPs chosen in previously published studies

Candidate SNP	Annotation	Proxy SNP	LD of proxy	OR	P_{meta}
rs1800734	MLH1-93G > A		Present on Hap300/Hap550 arrays	1.07	0.0726
rs1799977	MLH1 Ile219Val		Present on Hap300/Hap550 arrays	0.99	0.800
rs2303425	MSH2 -118T>C	rs10495944	r^2 = 0.95, D′ = 1.00	1.02	0.817
rs1981928	MSH2 intronic	rs3732183	r^2 = 1.00, D′ = 1.00	1.00	0.999
rs1042821	MSH6 Gly39Glu	rs6713506	r^2 = 0.30, D′ = 0.76	1.06	0.831
rs26279	MSH3 Ala1045Thr		Present on Hap300/Hap550 arrays	1.06	0.0814
rs1979005	MSH3 intronic	rs3776969	r^2 = 0.87, D′ = 1.00	0.94	0.370
rs1042522	TP53 Arg72Pro	rs7141	r^2 = 0.45, D′ = 0.88	1.01	0.837
rs1800056	ATM Phe858Leu	rs4987876	r^2 = 0.21, D′ = 1.00	0.97	0.636
rs2308321	MGMT Ile174Val		Present on Hap300/Hap550 arrays	1.00	0.989
rs25487	XRCC1 Gln399Arg	rs1799778	r^2 = 0.97, D′ = 1.00	0.98	0.488
rs3218536	XRCC2 R188H		Present on Hap300/Hap550 arrays	1.04	0.599
rs3218499	XRCC2 intronic	rs3218408	r^2 = 0.95, D′ = 1.00	0.99	0.868

Results shown are from the meta-analysis of the three GWAS data sets. Note that for rs26279, the direction of effect is opposite to that found in other studies.

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Table III

Summary of association studies undertaken for CHEK2 I157T and colorectal cancer risk

	Case Hets	Case Homs	Control Hets	Control Homs
Irmejs (34)	24	211	63	915
Kilpivaara (35)	76	896	100	1785
Cybulski (36)	88	1107	264	5232
Kleibl (37)	30	601	17	666
Konstantinova (38)	9	334	21	781

Numbers of cases and controls are shown for each study. Hets, I/T heterozygotes; Homs, common I/I homozygotes. In the meta-analysis, P_{het} = 0.77, I^2 = 0%.