Germline Variants and Advanced Colorectal Adenomas: Adenoma Prevention with Celecoxib Trial Genome-wide Association Study

Jiping Wang1, Luis G. Carvajal-Carmona3, Jen-Hwa Chu2, Ann G. Zauber4, APC Trial Collaborators, Michikai Kubo5, Koichi Matsuda5, Malcolm Dunlop6, Richard S. Houlston7, Oliver Sieber8, Lara Lipton8, Queenuke Nakamura5, Scott T. Weiss5, Ian Tomlinson9, and Monica M. Bertagnolli1

Abstract

Purpose: Identification of single-nucleotide polymorphisms (SNP) associated with development of advanced colorectal adenomas.

Experimental Design: Discovery phase: 1,406 Caucasian patients (139 advanced adenoma cases and 1,267 controls) from the Adenoma Prevention with Celecoxib (APC) trial were included in a genome-wide association study (GWAS) to identify variants associated with postpolypectomy disease recurrence. Genome-wide significance was defined as false discovery rate less than 0.05, unadjusted P = 7.4 × 10⁻⁷. Validation phase: results were further evaluated using 4,175 familial colorectal adenoma cases and 5,036 controls from patients of European ancestry [COloRectal Gene Identification consortium (CORGI), Scotland, Australia, and VQ58].

Results: Our study identified eight SNPs associated with advanced-adenoma risk in the APC trial (rs2837156, rs7278863, rs2837237, rs2837241, rs741864 at 21q22.2, and rs1381392 and rs17651822 at 3p24.1, at P < 10⁻⁷ level with OR > 2). Five variants in strong pairwise linkage disequilibrium (rs7278863, rs2837237, rs741864, and rs2837241; r² = 0.8–1) are in or near the coding region for the tight junction adhesion protein, IGSF5. An additional variant associated with advanced adenomas, rs1535989 [minor allele frequency, 0.11; OR, 2.09; 95% confidence interval (CI), 1.50–2.91], also predicted colorectal cancer development in a validation analysis (P = 0.019) using a series of adenoma cases or colorectal cancer (CORGI study) and 3 sets of colorectal cancer cases and controls (Scotland, VQ58, and Australia; N = 9,211).

Conclusions: Our results suggest that common polymorphisms contribute to the risk of developing advanced adenomas and might also contribute to the risk of developing colorectal cancer. The variant at rs1535989 may identify patients whose risk for neoplasia warrants increased colonoscopic surveillance. Clin Cancer Res; 19(23); 6430–7. ©2013 AACR.

Introduction

Colorectal cancer is a common malignancy, with prevalence in developed nations of 40 to 50 cases per 100,000 individuals (1). Approximately one-third of those diagnosed with colorectal cancer will die of their disease due to diagnosis at a stage not curable by locoregional therapy. Most colorectal cancer cases arise from premalignant adenomas that require years or even decades to progress to invasive disease. Colonoscopy to identify and remove precursor adenomas has been recommended for more than 25 years for patients at high colorectal cancer risk, and recently completed long-term analyses of screened cohorts confirmed the utility of adenoma removal for preventing deaths due to colorectal cancer (2).

Our goal is to understand the biology of colorectal cancer to develop effective prevention and therapy, and also to characterize individual risk in a manner that will identify patients most likely to benefit from colonoscopy to detect...
Identification of patients at highest risk of colorectal cancer is essential for providing optimal disease screening and prevention. This study uncovers germline susceptibility loci that indicate risk of disease and potential for improved understanding of disease biology.

The adenoma–carcinoma sequence in the colorectum represents a disease spectrum. Adenomas with a low risk of cancer development are small (<0.6 cm diameter) and lack histologic features associated with progression, such as the presence of villous features or high-grade dysplasia. The identification of an advanced adenoma (size ≥ 1 cm; villous or tubulovillous histology; high-grade dysplasia) indicates that a patient has a higher risk of future adenoma and colorectal cancer development (3). Advanced adenomas, therefore, are the most important lesions to target for colorectal cancer prevention. In this study, we used a large cohort of patients with adenoma from a prospective randomized clinical trial to identify single-nucleotide polymorphisms (SNP) associated with increased risk of developing advanced adenomas. These variants were then further tested using large genotyped cohorts of patients and controls with advanced adenomas and colorectal cancer. In doing so, we identified variants associated with both advanced premalignant lesions and colorectal cancer.

Materials and Methods

Study design and populations

The overall study design is illustrated in Fig. 1.

**Discovery phase.** Of note, 1,406 evaluable Caucasian patients were identified from the Adenoma Prevention with Celecoxib (APC) trial, a randomized, placebo-controlled study to test whether celecoxib reduced the occurrence of endoscopically detected colorectal adenomas. The endpoint advanced adenoma was defined as any adenoma with size 1 cm or more, villous/tubulovillous histology, or high-grade dysplasia. During the prospective follow-up period, 139 participants developed advanced adenomas identified during a scheduled colonoscopy screening examination. Detailed information about the trial design and primary outcomes was reported elsewhere (4).

**Validation phase.** The advanced adenoma susceptibility that SNPs identified from APC trial were further evaluated using genome-wide association study (GWAS) data from the following four nonoverlapping colorectal cancer case–control series of European ancestry (5).

1. CORGI: 931 familial colorectal adenoma or colorectal cancer cases and 929 cancer-free controls of White British origin ascertained through the CoLoRectal Gene Identification (CORGI) consortium. All cases had at least one first-degree relative with colorectal tumors and no mutations in the known highly penetrant colorectal cancer genes. Controls were spouses or partners of the cases and had no personal history of colorectal cancer (6).

2. Scotland: 1,003 early-onset Scottish colorectal cancer cases (<55 years) and 979 cancer-free Scottish population controls. Known Mendelian syndromes were excluded. Controls were matched by age (±5 years), gender, and area of residence (6).

3. VQ58: 1,800 British Stage II/III patients with colorectal cancer from the VICTOR (N = 923) and QUASAR2 (http://www.octo-oxford.org.uk/alltrials/trials/q2.html; N = 877) clinical trials, together with publicly available data from 2,690 population controls from the Wellcome Trust Case–Control Consortium (WTCCC) 1958 Birth Cohort (7).

**Translational Relevance**

Identification of patients at highest risk of colorectal cancer is essential for providing optimal disease screening and prevention. This study uncovers germline susceptibility loci that indicate risk of disease and potential for improved understanding of disease biology.

**Figure 1.** Study design. Including subjects with familial adenoma from CORGI. AA, advanced adenoma; CRC, colorectal cancer.
4. Australia: 441 colorectal cancer cases treated in the Royal Melbourne, Western and St Francis Xavier Cabrini Hospitals in Melbourne and 438 population controls from Brisbane Twin Nevus and Genes in Myopia studies, matched to the cases using principal component analysis (6).

Thus, 4,175 familial colorectal adenoma or colorectal cancer cases and 5,036 controls were included in the validation analysis. Human Subjects Committee approval to collect and genotype whole blood samples was obtained by Brigham and Women’s Hospital and the RIKEN Center for Genomic Medicine.

**Genotyping and quality control**

DNA was isolated from blood samples using standard methods and quantified with picogreen. For the APC cohort, genotyping was performed by the RIKEN Center for Genomic Medicine using the Illumina Human610-Quad BeadChip platform (Illumina). A White parent–child Centre d’Etude du Polymorphisme Humain (CEPH) trio from the HapMap was used to check for Mendelian transmission of alleles. \( \chi^2 \) test based on genotype frequencies at each SNP was used to test for deviations from Hardy–Weinberg equilibrium (HWE). Any SNP with HWE \( P < 0.001 \) was excluded. Two cases and two controls were randomly chosen as duplicates for quality control of genotype concordance. A total of 28 subjects and 1,792 markers were excluded for quality control reasons, including duplicates, those that showed identity-by-descent more than 12.5% or were gender mismatched, samples with less than 98%, and markers with less than 99% call rate or heterozygous haploids. The final Manhattan plot and QQ plot indicated the satisfactory quality control process (Supplementary Figs. S1 and S2).

**Figure 2.** LD analysis of SNPs on 21q22.2 and 7q32.3 by pairwise \( r^2 \). The 6 IGSF-5 related SNPs are within very tight linkage disequilibrium (LD) region.
For the additional susceptibility evaluation cohorts, samples were genotyped on Illumina Infinium SNP arrays, ranging from the Hap300 (for VQ58) to the Hap1M (for Australia). Details about genotyping and quality control for these studies have been provided previously (5). Ethics Committees approved these five studies and samples were collected in accordance with the tenets of the Declaration of Helsinki.

Among the top 19 SNPs identified from the APC trial, 12 SNPs had genotype data available from the CORGI, Scotland, VQ58, or Australia GWAS. Nine of these SNPs were typed in all four studies (rs1381392, rs17651822, rs17781398, rs16909065, rs9582985, rs2837156, rs2837241, and rs741864) and three were typed in three (rs1305889, rs1424593, and rs2837237; Supplementary Table S1).

Statistical analysis

To assess the strength of association between genotype and advanced-adenoma risk, a per allele unconditional ORs per allele ranging from 2.22 to 2.55. All six SNPs in the 21q22.2 region were located near the coding region for the adherens junction protein, IGSF5, and five of these SNPs (rs7278863, rs2837237, rs741864, rs741864, and rs2837241) were in strong linkage disequilibrium ($r^2 > 0.8$; Fig. 1). For the 3p24.1 signal, the OR for genotype rs1381392 was 2.01 (95% CI, 1.52–2.65; unadjusted $P = 7.4 \times 10^{-5}$), and that for rs17651822 was 2.16 (95% CI, 1.61–2.91; unadjusted $P = 2.1 \times 10^{-5}$).

Eleven SNPs (rs11886781 at 2p24.2, rs13085889 at 3p24.1, rs1381392, rs1424593, and rs7778725 at 7q32.3, rs16909065 and rs16909036 at 9q32.2, rs17654765, rs1535989, and rs9582985 at 13q33.2) were associated with moderate (~2-fold) ORs for advanced adenoma detection, but the associations did not reach genome-wide significance ($P \leq 10^{-7}$). Of these 11 SNPs,

### Table 1. APC trial advanced adenoma susceptibility loci

<table>
<thead>
<tr>
<th>Chromosome region</th>
<th>SNP</th>
<th>Position (bp)</th>
<th>Alleles</th>
<th>MAF</th>
<th>$P$</th>
<th>OR</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>2p24.2</td>
<td>rs11886781</td>
<td>18154780</td>
<td>A C</td>
<td>0.08</td>
<td>9.7E-06</td>
<td>2.25</td>
<td>KCNS3</td>
</tr>
<tr>
<td>3q22.2</td>
<td>rs13085889</td>
<td>135843760</td>
<td>A C</td>
<td>0.29</td>
<td>8.8E-06</td>
<td>1.77</td>
<td>EPHB1, KY</td>
</tr>
<tr>
<td>3p24.1</td>
<td>rs1381392</td>
<td>28724318</td>
<td>A G</td>
<td>0.18</td>
<td>7.4E-07</td>
<td>2.01</td>
<td>FAM188b</td>
</tr>
<tr>
<td>3p24.1</td>
<td>rs17651822</td>
<td>28695130</td>
<td>A C</td>
<td>0.14</td>
<td>2.1E-07</td>
<td>2.16</td>
<td>IGSF5</td>
</tr>
<tr>
<td>3p24.1</td>
<td>rs17781398</td>
<td>30807966</td>
<td>A G</td>
<td>0.10</td>
<td>9.0E-06</td>
<td>0.19</td>
<td>PLXNA4</td>
</tr>
<tr>
<td>7q32.3</td>
<td>rs1424593</td>
<td>131605541</td>
<td>C A</td>
<td>0.50</td>
<td>9.1E-06</td>
<td>0.56</td>
<td>PLXNA4</td>
</tr>
<tr>
<td>7q32.3</td>
<td>rs16909065</td>
<td>131602384</td>
<td>C A</td>
<td>0.49</td>
<td>8.6E-06</td>
<td>0.56</td>
<td>PLXNA4</td>
</tr>
<tr>
<td>7q32.3</td>
<td>rs7778725</td>
<td>131614938</td>
<td>G A</td>
<td>0.49</td>
<td>4.0E-06</td>
<td>0.55</td>
<td>PLXNA4</td>
</tr>
<tr>
<td>9q33.2</td>
<td>rs16909065</td>
<td>12159706</td>
<td>A G</td>
<td>0.05</td>
<td>3.6E-06</td>
<td>2.59</td>
<td>IGSF5</td>
</tr>
<tr>
<td>9q33.2</td>
<td>rs16909036</td>
<td>121587049</td>
<td>G A</td>
<td>0.05</td>
<td>3.7E-06</td>
<td>2.59</td>
<td>IGSF5</td>
</tr>
<tr>
<td>13q33.2</td>
<td>rs1535989</td>
<td>104820723</td>
<td>G A</td>
<td>0.11</td>
<td>8.9E-06</td>
<td>2.09</td>
<td>IGSF5</td>
</tr>
<tr>
<td>13q33.2</td>
<td>rs17654765</td>
<td>104820383</td>
<td>A G</td>
<td>0.10</td>
<td>4.7E-06</td>
<td>2.14</td>
<td>IGSF5</td>
</tr>
<tr>
<td>13q33.2</td>
<td>rs9582985</td>
<td>104821933</td>
<td>C A</td>
<td>0.11</td>
<td>9.3E-06</td>
<td>2.05</td>
<td>IGSF5</td>
</tr>
<tr>
<td>21q22.2</td>
<td>rs2837237</td>
<td>40048557</td>
<td>G A</td>
<td>0.12</td>
<td>3.2E-07</td>
<td>2.22</td>
<td>IGSF5</td>
</tr>
<tr>
<td>21q22.2</td>
<td>rs7278863</td>
<td>40087578</td>
<td>A G</td>
<td>0.10</td>
<td>1.4E-08</td>
<td>2.48</td>
<td>IGSF5</td>
</tr>
<tr>
<td>21q22.2</td>
<td>rs2837237</td>
<td>40119727</td>
<td>G A</td>
<td>0.12</td>
<td>3.6E-06</td>
<td>2.48</td>
<td>IGSF5</td>
</tr>
<tr>
<td>21q22.2</td>
<td>rs2837241</td>
<td>40130476</td>
<td>A C</td>
<td>0.12</td>
<td>3.7E-09</td>
<td>2.48</td>
<td>IGSF5</td>
</tr>
<tr>
<td>21q22.2</td>
<td>rs2837254</td>
<td>40143171</td>
<td>A G</td>
<td>0.11</td>
<td>2.9E-09</td>
<td>2.55</td>
<td>IGSF5</td>
</tr>
<tr>
<td>21q22.2</td>
<td>rs741864</td>
<td>40129665</td>
<td>A G</td>
<td>0.11</td>
<td>1.1E-08</td>
<td>2.48</td>
<td>IGSF5</td>
</tr>
</tbody>
</table>

*The total number of subjects is 1,406, of which 139 developed advanced adenomas.
six mapped to gene coding regions: rs11886781 to KCNS3, rs17781398 to FAM188b, rs13085889 to EPB11 and KY, and rs1424593, rs1364512, and rs77778725 all to PLXNA4 (Table 1 and Fig. 1). There are no comparable adenoma chemoprevention cohorts currently available for validation of the APC GWAS results. We therefore further examined APC trial results using GWAS data from four nonoverlapping colorectal cancer case-control series of European ancestry, one of which (CORGI) also included advanced adenoma cases (5). Among the 19 advanced-adenoma risk SNPs with a nominal significance level of P ≤ 10^{-6}, 12 were genotyped in at least three of the available four colorectal cancer GWA studies (Supplementary Table S1). Allelic frequencies of each variant and the corresponding associations with colorectal cancer phenotype were accessed in each of the four case-control samples. The results of the meta-analysis for overall associations with colorectal cancer phenotype were accessed (Table 2 and Supplementary Fig. S3).

One of the 19 SNPs identified in the APC trial, rs1535989, was replicated in the independent colorectal cancer cohorts, with an OR for colorectal cancer development of 1.12 (95% CI, 1.019–1.23; P = 0.019). There was no evidence of inter-study heterogeneity (P_{het} = 0.71; I^2 = 0%). An additional exploratory meta-analysis was performed, combining all five studies and using either advanced adenoma or colorectal cancer as the outcome (Table 2). SNP rs9582985 originally identified in the APC cohort showed marginally significant association with outcome (OR, 1.11; P = 0.055).

Clinical data from the APC trial were used to further characterize rs1535989 by examining the association of this variant with other susceptibility factors for advanced colorectal neoplasia, including age, sex, aspirin use at baseline, family history of colorectal cancer, and on-study treatment with celecoxib. SNP and environmental factors interaction terms were included in the model. SNP rs1535989 showed statistically significant interactions with subjects’ age (P = 0.0016), sex (P = 0.0057), and aspirin use at baseline (P = 0.02). The associations with advanced neoplasia were stronger in older individuals (>60; OR, 3.20; 95% CI, 2.10–4.87), males (OR, 2.74; 95% CI, 1.89–3.97), and those using aspirin at baseline (OR, 3.63; 95% CI, 2.06–6.40; Table 3). There were no statistically significant interactions with colorectal cancer family history or on-study treatment with celecoxib.

### Discussion

Among the approximately 145,000 colorectal cancer cases diagnosed per year in the United States, only 5% represent autosomal dominant predisposition syndromes, with the majority of these involving either hereditary non-polyposis colon cancer (HNPCC) or familial adenomatous polyposis (FAP). An additional 20% to 25% of colorectal cancer cases show a familial association without precise genetic characterization, and the majority of colorectal cancers occur in individuals without a family history of the disease. Self-reported family history does not accurately

#### Table 2. Meta-analysis using adenoma or colorectal cancer as a composite outcome

<table>
<thead>
<tr>
<th>SNP</th>
<th>N</th>
<th>P</th>
<th>P(R)</th>
<th>OR</th>
<th>OR(R)</th>
<th>Q</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs13085889</td>
<td>4</td>
<td>0.1048</td>
<td>0.1048</td>
<td>1.0575</td>
<td>1.0575</td>
<td>0.5438</td>
<td>0</td>
</tr>
<tr>
<td>rs1381992</td>
<td>4</td>
<td>0.4636</td>
<td>0.4636</td>
<td>1.0295</td>
<td>1.0295</td>
<td>0.4186</td>
<td>0</td>
</tr>
<tr>
<td>rs1424593</td>
<td>3</td>
<td>0.405</td>
<td>0.405</td>
<td>1.027</td>
<td>1.027</td>
<td>0.4233</td>
<td>0</td>
</tr>
<tr>
<td>rs1535989</td>
<td>4</td>
<td>0.012</td>
<td>0.012</td>
<td>1.1304</td>
<td>1.1304</td>
<td>0.7925</td>
<td>0</td>
</tr>
<tr>
<td>rs16909065</td>
<td>4</td>
<td>0.1273</td>
<td>0.1273</td>
<td>0.9054</td>
<td>0.9054</td>
<td>0.498</td>
<td>0</td>
</tr>
<tr>
<td>rs17651822</td>
<td>4</td>
<td>0.689</td>
<td>0.689</td>
<td>1.0176</td>
<td>1.0176</td>
<td>0.8499</td>
<td>0</td>
</tr>
<tr>
<td>rs17781398</td>
<td>4</td>
<td>0.7972</td>
<td>0.7972</td>
<td>1.016</td>
<td>1.016</td>
<td>0.9487</td>
<td>0</td>
</tr>
<tr>
<td>rs2837156</td>
<td>4</td>
<td>0.8017</td>
<td>0.8017</td>
<td>0.9881</td>
<td>0.9881</td>
<td>0.4326</td>
<td>0</td>
</tr>
<tr>
<td>rs2837210</td>
<td>4</td>
<td>0.8706</td>
<td>0.9766</td>
<td>1.0083</td>
<td>0.9983</td>
<td>0.3114</td>
<td>16.05</td>
</tr>
<tr>
<td>rs2837237</td>
<td>4</td>
<td>0.3464</td>
<td>0.3464</td>
<td>0.9379</td>
<td>0.9379</td>
<td>0.4326</td>
<td>0</td>
</tr>
<tr>
<td>rs2837241</td>
<td>4</td>
<td>0.938</td>
<td>0.8585</td>
<td>0.9963</td>
<td>0.9907</td>
<td>0.3395</td>
<td>10.69</td>
</tr>
<tr>
<td>rs741864</td>
<td>4</td>
<td>0.6248</td>
<td>0.6248</td>
<td>0.971</td>
<td>0.971</td>
<td>0.6068</td>
<td>0</td>
</tr>
<tr>
<td>rs9582985</td>
<td>4</td>
<td>0.05468</td>
<td>0.05468</td>
<td>1.1188</td>
<td>1.1188</td>
<td>0.9416</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Table 3. Genotype-phenotype/environment interactions for SNP rs1535989

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>OR</th>
<th>Interaction (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.91 (0.42–1.76)</td>
<td>0.0016</td>
</tr>
<tr>
<td>&gt;60</td>
<td>3.20 (2.10–4.87)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.65 (0.25–1.68)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Male</td>
<td>2.74 (1.89–3.97)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.23 (1.51–3.28)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Yes</td>
<td>1.74 (0.88–3.43)</td>
<td>0.53</td>
</tr>
<tr>
<td>Prior aspirin use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.58 (1.03–2.42)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Yes</td>
<td>3.63 (2.06–6.40)</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.63 (1.03–2.58)</td>
<td>0.0016</td>
</tr>
<tr>
<td>200 mg</td>
<td>2.51 (1.27–4.95)</td>
<td>0.0016</td>
</tr>
<tr>
<td>400 mg</td>
<td>2.43 (1.16–5.07)</td>
<td>NS</td>
</tr>
</tbody>
</table>
assess the inherited risk of advanced adenomas because patients’ knowledge of their family history of colorectal adenomas is often unknown or incomplete (10). Recent GWAS from members of this collaboration have identified 18 colorectal cancer susceptibility variants with minor allele frequencies ranging from 0.07 to 0.48 that each convey a small degree of risk modification (OR per allele, 0.87–1.35; refs. 11–15). The results presented here expand these data to address inherited susceptibility for developing advanced adenomas that represent targets for colorectal cancer prevention. In addition to the studies whose data were used here, there have been a number of other GWAS with colorectal cancer or colorectal adenomas as the primary phenotype (16–20). These have yielded a substantial number of possible susceptibility variants, most conveying modestly altered risk. A recent case–control meta-analysis from 14 studies identified SNPs on 2q32.3 (rs11903757), 1q25.3 (rs10911251), 12p13.32 (rs3217810), and 12q24.21 (rs59336) that represented ORs ranging from 0.84 to 1.15 (16).

The APC trial was designed to determine whether the selective cyclooxygenase-2 inhibitor, celecoxib, prevents adenomas in patients at high risk for colorectal cancer. Eligibility criteria required that participants have at least one prior adenoma >6 mm in size, or multiple adenomas. During the 5 years of endoscopic surveillance, 21.3% of APC trial participants randomized to placebo developed recurrent advanced adenomas (21). This rate was decreased to 12.5% in patients receiving celecoxib 200 mg twice daily (P < 0.0001). However, concerns over cardiovascular toxicity currently prohibit the use of celecoxib for routine colorectal cancer chemoprevention (22). Results presented here showed that advanced adenomas were twice as likely to occur in APC trial participants with variant rs1535989, and that this increased risk was not affected by celecoxib treatment. For males or older individuals, the risk was more than 3-fold higher than that for females or participants younger than 60. The observed interaction between baseline aspirin use and advanced-adenoma risk is particularly interesting. Aspirin use reduces the incidence of colorectal adenomas and colorectal cancer, and subjects enrolled in the APC trial who used aspirin at baseline were those who developed adenomas despite aspirin use. These individuals may therefore have constituted a higher risk subset because they were relatively resistant to aspirin chemoprevention. The analyses conducted here showed that APC trial participants who both developed adenomas while taking aspirin and had variant rs1535989 demonstrated a 3.63-fold increase in advanced-adenoma risk during surveillance. If this association can be confirmed in other studies, and other variants of similar effect are found, then genotyping will represent a useful method to target high-risk patients for preventive treatments including more frequent colonoscopic screening.

Additional results from this GWAS suggest areas for further research about the molecular basis of colorectal neoplasia. Variants at rs2837156, rs7278863, rs2837237, rs2837241, rs2837254, and rs741864 are in close association with advanced adenoma risk during surveillance. If this association can be confirmed in other studies, and other datasets to evaluate their association with colorectal cancer were not excluded from replication datasets. This might under/overestimate the association between identified SNPs and sporadic colorectal-cancer risks.

In summary, this study identified 19 SNPs associated with advanced-adenoma risk at a level of P ≤ 10^{-6}. Of these, 12 SNPs were tested in a meta-analysis using independent datasets to evaluate their association with colorectal cancer development, and rs1535989 was also associated with increased risk of both advanced adenomas and colorectal cancer. In addition, eight of the variants identified in the APC trial mapped to coding regions of genes previously implicated in colorectal cancer progression, and warrant further study to confirm their role in modifying tissue-specific biologic function.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: J. Wang, L.G. Carvajal-Carmona, A.G. Zauber, APC Trial Collaborators, M. Kubo, M.J. Raitan, I. Tomilinson, M.M. Bertagnolli

Development of methodology: J. Wang, A.G. Zauber, APC Trial Collaborators, M.M. Bertagnolli

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.G. Carvajal-Carmona, APC Trial Collaborators, M. Kubo, K. Matsuda, M. Dunlop, R.S. Houlston, O. Sieber, L. Lipton, P. Gibbs,
Acknowledgments

The authors thank all the individuals who participated in the various studies. This study made use of genotyping data on the 1958 Birth Cohort. Support: Clinical Cancer Research (CA-N01-22-010) and the Wellcome Trust Case-Control Consortium 2; a full list of the CONCOR investigators and CONCOX collaborators. This study made use of genotyping data on the 1958 Birth Cohort.


Statistical revision: J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

N.G. Martin, W.G. Montgomery, J.A. Maitland, M.M. Bertagnolli

Writing, review, and/or revision of the manuscript: J. Wang, L.G. Carvajal-Carmona, J.H. Chu, A.G. Zauber, J. Young, P.N. Baird, M.J. Raita, S.T. Weiss, I. Tomlinson, M.M. Bertagnolli

Statistical revision: J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli


Acknowledgments

The authors thank all the individuals who participated in the various studies. This study made use of genotyping data on the 1958 Birth Cohort and the Wellcome Trust Case-Control Consortium 2; a full list of the CONCOR investigators and CONCOX collaborators. This study made use of genotyping data on the 1958 Birth Cohort.


Statistical revision: J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

N.G. Martin, W.G. Montgomery, J.A. Maitland, M.M. Bertagnolli

Writing, review, and/or revision of the manuscript: J. Wang, L.G. Carvajal-Carmona, J.H. Chu, A.G. Zauber, J. Young, P.N. Baird, M.J. Raita, S.T. Weiss, I. Tomlinson, M.M. Bertagnolli

Statistical revision: J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli


J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli


J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

Acknowledgments

The authors thank all the individuals who participated in the various studies. This study made use of genotyping data on the 1958 Birth Cohort and the Wellcome Trust Case-Control Consortium 2; a full list of the CONCOR investigators and CONCOX collaborators. This study made use of genotyping data on the 1958 Birth Cohort.


Statistical revision: J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

Acknowledgments

The authors thank all the individuals who participated in the various studies. This study made use of genotyping data on the 1958 Birth Cohort and the Wellcome Trust Case-Control Consortium 2; a full list of the CONCOR investigators and CONCOX collaborators. This study made use of genotyping data on the 1958 Birth Cohort.


Statistical revision: J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli

J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli


J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli


J. Wang, M. Kubo, G.W. Montgomery, S.T. Weiss, M.M. Bertagnolli
National Cancer Research Network supported the NSCCG. M. Dunlop received from the Medical Research Council (G0000657–53203), CORE and Scottish Executive Chief Scientist’s Office (K/OPR/2/2/333, C28/4/449). The Colon Cancer Family Registry was supported by the National Cancer Institute, NIH under Request for Application CA-95-011, and through cooperative agreements with the Australasian Colorectal Cancer Family Registry (U01 CA097775), the ISC: Familial Colorectal Neoplasia Collaboration Group (U01 CA074797), Mayo Clinic Cooperative Family Registry for Colon Cancer Studies (U10 CA074800), Ontario Registry for Studies of Familial Colorectal Cancer (U01 CA074783), Seattle Colorectal Cancer Family Registry (U01 CA074794), and The University of Hawaii Colorectal Cancer Family Registry (U01 CA074806). P.N. Baird is supported by Australian National Health and Medical Research Council Senior Research Fellowship #1028444. CERA receives Operational Infrastructure Support from the Victorian Government, Australia.

This study was supported by NCI N01-95015 and HHSN261201000082C (to M.M. Bertagnolli, A.G. Zauber, and J. Wang), U01GM61393 (to M.J. Ratain), U01GM61390, and the Biobank Japan Project funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology. This work is part of the NIH Pharmacogenomics Research Network-RIKEN Center for Genomic Medicine Global Alliance. Pfizer, Inc. partially funded the APC Trial. L.G. Carvajal-Carmona and I. Tomlinson received support from Cancer Research UK and the Oxford Comprehensive Biomedical Research Centre, and the European Union (FP7 CHIBCHA Consortium). The Wellcome Trust Centre for Human Genetics is supported by a Wellcome Trust Core Grant 090532/Z/09/Z.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received March 2, 2013; revised September 21, 2013; accepted September 24, 2013; published OnlineFirst October 1, 2013.

References

Germline Variants and Advanced Colorectal Adenomas: Adenoma Prevention with Celecoxib Trial Genome-wide Association Study


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-13-0550

Cited articles
This article cites 27 articles, 5 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/19/23/6430.full#ref-list-1

Citing articles
This article has been cited by 2 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/19/23/6430.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.