Familial Colorectal Cancer and Genetic Susceptibility: Colorectal Risk Variants in First-Degree Relatives of Patients With Colorectal Cancer

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INTRODUCTION: Epidemiological studies estimate that having a first-degree relative (FDR) with colorectal cancer (CRC) increases 2-fold to 3-fold the risk of developing the disease. Because FDRs of CRC patients are more likely to co-inherit CRC risk variants, we aimed to evaluate potential differences in genotype distribution of single nucleotide polymorphisms (SNPs) related to CRC risk between FDRs of patients with nonsyndromic CRC (cases) and individuals with no family history of CRC (controls).

METHODS: We designed a case-control study comprising 750 cases and 750 Spanish Caucasian controls matched by sex, age, and histological findings after colonoscopy. Genomic DNA from all participants was genotyped for 88 SNPs associated with CRC risk using the MassArray (Sequenom) platform.

RESULTS: Ten of the 88 SNPs analyzed revealed significant associations ($P<0.05$) with a family history of CRC in our population. The most robust associations were found for the rs17094983G>A SNP in the long noncoding RNA LINC01500 (odds ratio = 0.72; 95% confidence interval: 0.58–0.88, log-additive model), and the rs11255841T>A SNP in the long noncoding RNA LINC00709 (odds ratio = 2.04; 95% confidence interval: 1.19–3.51, dominant model). Of interest, the observed associations were in the same direction than those reported for CRC risk.

DISCUSSION: FDRs of CRC patients show significant differences in genotype distribution of SNPs related to CRC risk as compared to individuals with no family history of CRC. Genotyping of CRC risk variants in FDRs of CRC patients may help to identify subjects at risk that would benefit from stricter surveillance and CRC screening programs.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A497

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INTRODUCTION

Colorectal cancer (CRC) is a multifactorial disease resulting from complex interactions between environmental and genetic factors. Although most cases of CRC correspond to sporadic forms, approximately 25%–30% of all cases occur in patients with a family history of CRC. Only a small fraction (2%–8%) of those CRC arises in the setting of the highly penetrant inherited syndromes due to germline mutations in well-known genes. The main subtypes of hereditary CRC are hereditary nonpolyposis CRC and familial adenomatous polyposis. Aside from these, there is a significant number of CRCs in which a strong family aggregation is observed but do not show a defined Mendelian inheritance pattern. It is termed familial CRC to distinguish it from the above well-established hereditary syndromes (1).

Over the past 2 decades, genome-wide association studies (GWAS) (2–17) and candidate gene analysis (18,19) have identified multiple gene variants, mainly single nucleotide polymorphisms (SNPs), associated with susceptibility to CRC. The risk conferred by each of these variants located in low penetration genes is usually modest. However, the combination of several risk variants in a polygenic model has been reported to increase the risk of CRC in an additive or exponential way. Despite the large

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number of association studies, very few have point out the relevance of gene polymorphisms in the so-called nonsyndromic familial CRC.

From a clinical point of view, the risk of developing familial CRC depends mainly on 3 factors: (i) the number of affected relatives, (ii) the degree of relationship, and (iii) the age at diagnosis of CRC in the affected family member (1). Epidemiological studies estimate that having a first-degree relative (FDR) with CRC increases 2-fold to 3-fold the lifetime risk of developing CRC (20–22). Taking into account that FDRs share the genome with a CRC patient in the same family (parents, offspring, and siblings), it is rational to think that FDRs of patients with CRC would have a higher probability of presenting a co-inheritance of multiple common risk variants in low penetrance genes that would provide them a greater risk of developing CRC and precancerous lesions as compared to individuals with no family history of CRC.

Trying to address this issue, we design a case-control study to evaluate potential differences in the distribution of genotypes and allele frequencies of a panel of selected SNPs related to CRC and adenoma risk between FDRs of patients with CRC (cases) and individuals with no family history of CRC (controls).

PATIENTS AND METHODS

Patients

The study design and data collection methods have been described in detail previously (23). Briefly, this is a case–control study simultaneously conducted in 2 general hospitals integrated into the Spanish National Health System. A total of 1,500 subjects (750 cases and 750 controls) were recruited at the University Hospital Lozano Blesa of Zaragoza and the University Hospital of the Canary Islands in Tenerife from May 2010 to May 2014.

Cases were selected from the CRC screening programs in Zaragoza and Tenerife and comprised 750 Spanish White FDRs of patients with nonsyndromic CRC. The control group consisted of 750 individuals with no family history of CRC recruited from those patients who were scheduled for colonoscopy at hospitals either by symptoms or by CRC screening in the average-risk population. Cases and controls were matched by sex, age (±5 years), and histological lesions found during colonoscopy. Patients were stratified in 3 groups based on the endoscopic findings and pathology review: (i) patients with no lesions or with no neoplastic lesions; (ii) patients with low-risk adenomas (LRAs), defined as <3 nonadvanced adenomas; and (iii) patients with high-risk adenomas (HRAs), defined as advanced adenomas or ≥3 non-advanced adenomas. Adenomas were classified as advanced if they were ≥10 mm in size or had ≥20% villous components or high-grade dysplasia. Designation as LRA or HRA was based on the likelihood of developing advanced neoplasia during surveillance after polypectomy as recommended by the American and European Societies of Gastrointestinal Endoscopy (24,25).

Information concerning demographic characteristics and potential risk factors including family history of CRC (any reported CRC in FDRs or 2 or more CRC cases in second-degree relatives [SDRs]), smoking habit, alcohol consumption, and chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) was obtained using a questionnaire administered by trained personnel as previously described (23).

After completion of the interview, 10 mL of peripheral blood from each patient was collected into Ethylenediaminetetraacetic acid tubes for subsequent DNA extraction. Once processed, whole blood samples were aliquoted and stored at −80 °C until use. All subjects gave written informed consent to the study, which was conducted in accordance with the Ethical Committee of the participating Hospitals.

SNP selection and genotyping methods

Genomic DNA was extracted from Ethylenediaminetetraacetic acid–preserved whole blood using the automated DNA isolation system AutoGenFlex 3000. DNA samples were aliquoted and stored at 4 °C until analysis.

The panel of 99 SNPs included in our study was selected from the NCBI database (http://www.ncbi.nlm.nih.gov/snp) and the NHGRI-EBI GWAS Catalog (http://www.ebi.ac.uk/gwas) based on 3 main criteria: (i) published evidence of an association with CRC or adenoma risk by GWAS of candidate gene studies, (ii) having reported a minor allele frequency ≥ 1% in Whites, or (iii) having potential functional consequences leading to altered protein concentrations or protein functions. Genotyping was performed at the Spanish National Genotyping Centre (CEGEN-Santiago de Compostela) using the Sequenom MassARRAY iPLEX platform. For quality control, intraplate and interplate duplicates were included. Genotype concordance was 100% for all samples. The post-genotype quality control comprised the exclusion of 11 SNPs due to failure of genotyping (rs11632715, rs17730929, PTGS1 rs3842787, and PNMAL1 rs7248888), a call rate < 95% (TPH2 rs10879357, MYRF rs174537, PTGS2 rs20417, ERCC2 rs1799793, and HADC9 rs1913914), or lack of Hardy-Weinberg equilibrium in controls (Fisher test P < 10−4, rs11671104, rs2965667). Finally, 88 SNPs (see Supplementary Table S1, Supplementary Digital Content 1, http://links.lww.com/CTG/A497) were successfully genotyped in our population and remained available for statistical analysis.

Statistical analysis

Continuous variables were expressed as means with SD, whereas qualitative variables were expressed as frequencies and percentages. The relationship between qualitative variables was evaluated by contingency tables with χ² tests.

Concerning gene polymorphisms, genotype frequencies for each SNP in controls were tested for Hardy-Weinberg equilibrium by a χ² test with one degree of freedom (df). Genotype and allele frequencies between cases and controls were compared using the χ² test with Yates’ correction or Fisher exact tests. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each genetic variant using the SNPassoc package implemented in R 3.2.2. Univariate and logistic regression analyses were evaluated under codominant, dominant, recessive, overdominant, and log-additive genetic models. The best-fitting genetic model was selected using the Akaike information criteria. For all tests, a 2-sided P value < 0.05 was considered statistically significant. To address the issue of conducting multiple comparisons, the False Discovery Rate method was applied. The statistical analysis was performed using the SPSS software v 22.0 for Windows (SPSS Ibérica, Madrid, Spain).

Based on the frequencies of the analyzed SNPs in our population, the size of the study was sufficient to detect ORs > 1.41 or < 0.73 with a power of 80% and a α value of 0.05. For the less prevalent polymorphisms (minor allele frequency: 0.01–0.10), the study had a power of 80% to detect ORs > 4.85 in the whole data set. Power calculations were estimated using the program Epidat 4.1.
RESULTS
Clinical and demographic characteristics of patients
Table 1 summarizes the demographic and clinical characteristics of cases (FDRs of patients with CRC) and controls (individuals with no family history of CRC). No significant differences between cases and controls were observed regarding consumption of tobacco, alcohol, and chronic use of NSAIDs or low-dose ASA.

In relation to the endoscopic findings, 57% of the patients (429 cases and 429 controls) showed no neoplastic lesions, 288 patients (144 cases and 144 controls) had LRA, and 354 patients (177 cases and 177 controls) had HRA.

Family history of CRC
In our study, subjects referred as cases (n = 750) had at least one FDR affected with CRC. The distribution of cases according to the number of affected FDRs and the age at diagnosis of CRC in the affected relative is shown in Figure 1. Most cases (89.3%) had one FDR with CRC, 10.5% had 2 FDR with CRC, and 20.1% of cases had both, FDRs and SDRs with CRC. Parents were the most often affected FDRs (68.8%), followed by siblings (30.5%) and children (0.6%). Concerning SDRs, uncles were the most often affected (54.9%), followed by grandparents (21.5%) and cousins (11.5%).

When patients were stratified according to histological findings, we found that cases with 2 FDRs with CRC were significantly more frequent in the group of patients with adenomas (HRA or LRA) than that in the group of patients with non-neoplastic lesions (14.3% vs 7.9%, OR = 1.9; 95% CI: 1.2–3.1, P = 0.005).

Gene polymorphisms and family history of CRC
A total of 1,500 subjects (750 cases and 750 controls) were successfully genotyped for a panel of 88 SNPs previously related to CRC risk. Genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium in the control group (Fisher test, P > 10^-4) (see Supplementary Table S1, Supplementary Digital Content 1, http://links.lww.com/CTG/A497).

In our population, 10 SNPs (rs1136410, rs12917, rs13343954, rs16940, rs16973225, rs17094983, rs39453, rs4939827, and rs73376930) revealed significant associations (P < 0.05) with a family history of CRC in at least one of the 5 genetic models evaluated in the analysis (Table 2). After False Discovery Rate multiple test correction, only the rs17094983 SNP in the long noncoding RNA (lncRNA) LINCO1500 gene retained statistical significance. Thus, the frequency of the rs17094983 minor allele A was significantly lower in FDRs of CRC patients than that in controls (log-additive model, OR = 0.72; 95% CI: 0.58–0.89, Q value = 0.037) (Table 2).

Stratified analysis by histological type of adenoma (LRA/HRA) showed additional differences in genotype distribution and allele frequencies between cases and controls. Table 3 summarizes

| Table 1. Demographic and clinical characteristics of the study population |
|-------------------------------------------------------------|
| **Cases (n = 750), n (%)**                                   |
| **Age**                                                     |
| Mean (SD)                                                   | 54.4 (9.2) |
| Median (range)                                              | 55.0 (30–84) |
| **Sex**                                                     |
| Male                                                        | 362 (48.3) |
| Female                                                      | 388 (51.7) |
| **Alcohol**                                                 |
| No                                                          | 421 (56.1) |
| Yes                                                         | 291 (38.8) |
| Unknown                                                     | 38 (5.1) |
| **Tobacco**                                                 |
| Never smoker                                                | 393 (52.4) |
| Current smoker                                              | 184 (24.5) |
| Former smoker                                               | 149 (19.9) |
| Unknown                                                     | 24 (3.2) |
| **Chronic use of NSAIDs**                                   |
| Yes                                                         | 43 (5.7) |
| No                                                          | 704 (93.9) |
| Unknown                                                     | 3 (0.4) |
| **Chronic use of low-dose (≤300 mg) ASA**                   |
| Yes                                                         | 34 (4.5) |
| No                                                          | 621 (82.8) |
| Unknown                                                     | 95 (12.7) |

ASA, acetylsalicylic acid; n, number of individuals; NSAID, non-steroidal anti-inflammatory drug.
those SNPs significantly associated with family history of CRC in the multivariate analysis adjusted by age, sex, tobacco, alcohol, and drug use (NSAIDs and low-dose ASA). Three SNPs located in the lncRNA LINC00709 (rs11255841T>A, rs10795668G>A) and MLH1 (rs1800734G>A) genes were significantly associated with susceptibility to family history of CRC in the group of patients with LRAs. Similarly, the rs39453T variant was found to be more frequent in FDRs of CRC patients than that in controls in the subgroup of patients with HRA (log-additive model, OR = 1.63; 95% CI: 1.12–2.36). However, after applying the False Discovery Rate method, only the rs11255841A variant were significantly more frequent in cases than that in controls in the group of patients with LRA (49.7% vs 36.8%; dominant model, OR = 2.04; 95% CI: 1.19–3.51).

**DISCUSSION**

Epidemiological studies estimate that having a FDR with CRC increases 2-fold to 3-fold the risk of developing CRC (20–22). Because FDRs share the genome and the genetic risk background of their affected relative (parents, offspring, and siblings), it is rational to think that FDRs of patients with CRC have a higher probability of presenting a co-inheritance of multiple risk variants that would provide them a greater risk of developing CRC as compared to subjects with no family history of CRC. Based on this hypothesis, we designed a case–control study to assess potential differences in genotype and allele distribution of 88 SNPs related to CRC risk between FDRs of patients with CRC (cases) and individuals with no family history of CRC (controls). The most robust association in our study was observed for the intronic variant rs17094983G>A (LINC01500) located in the 14q23.1 chromosomal region. This SNP was firstly reported as associated with CRC risk in a GWAS performed in 2013 by Peters et al. (11). According to the authors, the minor allele (A) of rs17094983 was associated with a lower risk of developing CRC (P < 3 × 10^{-10}), although this association did not reach genome-wide significance levels. A subsequent GWAS by Lemire et al. (26) corroborated the protective effect of the rs17094983A variant in the development of CRC in both, African and White populations (P = 2.5 × 10^{-10}), reaching in the later, significance levels required in GWAS studies. Unlike the study of Peters, Lemire et al. (26) did not include as controls individuals having a family history of CRC because they considered FDRs of patients with CRC as an

![Figure 1. Distribution of cases according to the number of FDRs affected and the age at diagnosis of colorectal cancer (CRC). Most cases had one FDR with CRC diagnosed younger than or equal to 60 years (63.6%, 477/750) or younger than 60 years (25.6%, 192/750). Seventy-nine cases (10.5%) had 2 FDRs with CRC, and only one case had 3 FDRs with CRC.](image)

**Table 2. SNPs associated with family history of colorectal cancer in the study population**

| Db SNP ID | Gene   | Chr | SNP type | Controls genotype, n = 750 | Cases genotype, n = 750 | Genetic modela | ORb  | 95% Clb  | P-value | Q-valuec |
|-----------|--------|-----|----------|---------------------------|--------------------------|----------------|-------|----------|---------|----------|
| rs1136410 | PARP1  | 1   | V762A    | AA 567 163 17 AA 575 162 5 | Aa 170 15 24 Aa 174 14 3 | Recessive       | 0.35  | 0.13–0.96 | 0.027   | 0.070    |
| rs1800734 | MLH1   | 3   | Upstream | G/A 463 247 38 424 271 53 | Gg 205 20 4 Gg 215 21 3 | Log-additive    | 1.27  | 1.06–1.51 | 0.009   | 0.078    |
| rs39453   | OSBPL3/CYCS | 7 | Intergenic | T/C 357 313 80 310 351 88 | Tt 188 13 3 Tt 201 12 4 | Log-additive    | 1.20  | 1.02–1.41 | 0.028   | 0.117    |
| rs12917   | MGMT   | 10  | L115F    | C/T 536 204 10 524 202 23 | Cc 245 20 4Cc 250 20 3 | Recessive       | 2.39  | 1.10–5.18 | 0.023   | 0.070    |
| rs17094983| LINC01500 | 14 | Intronic | G/A 508 213 27 558 174 15 | Ga 230 20 3 Ga 238 20 3 | Log-additive    | 0.72  | 0.58–0.89 | 0.002   | **0.037** |
| rs16973225| LOC102724001 | 15 | Intronic | A/C 640 107 1 665 76 7 | Ac 390 14 3 Ac 403 13 4 | Dominant        | 0.71  | 0.51–0.99 | 0.044   | 0.149    |
| rs73376930| GREM1  | 15  | Intronic | A/G 514 215 21 481 239 30 | Ag 257 20 4Ag 265 20 3 | Log-additive    | 1.25  | 1.03–1.53 | 0.026   | 0.117    |
| rs16940   | BRCA1  | 17  | L724L    | A/G 302 370 76 340 319 89 | Ag 160 14 3 Ag 168 14 3 | Overdominant    | 0.75  | 0.61–0.94 | 0.011   | 0.088    |
| rs4939827 | SMAD7  | 18  | Intronic  | T/C 240 348 162 242 381 126 | Tt 124 14 3 Tt 130 14 4 | Recessive       | 0.73  | 0.55–0.96 | 0.023   | 0.070    |
| rs13343954| RHPN2  | 19  | Intronic  | T/C 548 180 21 539 199 10 | Tt 270 20 4Tt 276 20 3 | Recessive       | 0.42  | 0.18–1.01 | 0.040   | 0.070    |

The bold with italicized allele represents the colorectal cancer risk allele.

A/a, major/minor alleles; Chr, chromosome number; CI, confidence interval; n, number of individuals; OR, odds ratio; SNP, single nucleotide polymorphism.

aThe best-fitting genetic model was selected using the Akaike information criteria.

bORs and 95% CIs were calculated by logistic regression analysis adjusted by age, sex, tobacco, alcohol, drugs use (non-steroidal anti-inflammatory drugs and low-dose acetylsalicylic acid), and histological lesion.

cQ-values were obtained after applying the False Discovery Rate method for multiple comparisons. Q-values < 0.05 are highlighted in bold.
intermediate step between CRC and healthy subjects with no family history of CRC. In line with their findings, the frequency of the rs17094983 allele A in our study was significantly lower in FDRs of patients with CRC than that in controls (log-additive model, OR 0.72; 95% CI: 0.58–0.89, Q value = 0.037). Based on these results, we could speculate that the rs17094983A variant, identified in GWAS as a protective factor of CRC, would be in turn inversely associated with the risk of having a positive family history of CRC. This hypothesis is also biologically plausible in the light of the putative functional effect of the rs17094983 SNP.

Some studies have reported the link between rs17094983 genotypes and variations in the expression of the RTN1 (Reticulon 1) gene.

### Table 3. SNPs associated with family history of colorectal cancer: stratified analysis by subtype of adenomas

| Db SNP ID | Gene            | Chr | SNP type | A/a   | Controls genotype | Cases genotype | Genetic modela | Multivariate analysis | ORb   | 95% CIb | P-value | Q-valuec |
|----------|-----------------|-----|----------|-------|-------------------|----------------|-----------------|-----------------------|-------|---------|---------|----------|
|          |                 |     |          |       |       | AA  | Aa | aa | AA  | Aa | aa | Dominant          |       |          |         |          |
| rs1800734 | MLH1            | 3   | Upstream | G/A   | 93    | 42  | 9  | 77 | 55  | 11 | Dominant          | 2.14  | 1.23–3.71 | 0.006  | 0.403    |
| rs11255841| LINC00709       | 10  | Intronic | T/A   | 91    | 42  | 11 | 72 | 68  | 3  | Dominant          | 2.04  | 1.19–3.51 | 0.001  | 0.024    |
| rs10795668| LINC00709       | 10  | Intronic | G/A   | 86    | 44  | 14 | 67 | 71  | 6  | Codominant        | 2.38  | 1.35–4.20 | 0.001  | 0.059    |

A/a, major/minor alleles; Chr, chromosome number; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

aThe best-fitting genetic model was selected using the Akaike information criteria.

bORs and 95% CIs were calculated by logistic regression analysis adjusted by age, sex, tobacco, alcohol, drugs use (nonsteroidal anti-inflammatory drugs and low-dose acetylsalicylic acid), and histological lesion.

cQ values were obtained after applying the False Discovery Rate method for multiple comparisons. Q-values < 0.05 are highlighted in bold.

Figure 2. Proposal of colorectal cancer screening algorithm. *Positive results on FIT should be followed up with timely colonoscopy. CRC, colorectal cancer; FDR, first-degree relative; FIT, fecal immunochemical test; IBD, inflammatory bowel disease; SNP, single nucleotide polymorphism.

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gene (26). The RTN1 gene encodes the synthesis of 3 proteins (RTN1-A, RTN1-B, and RTN1-C), localized in the endoplasmic reticulum membrane, that play a dominant regulatory role in the control of apoptosis and cell proliferation (27). It has been shown that individuals heterozygous for the rs17094971 A>T variant in strong linkage disequilibrium with rs17094983 (r² = 0.81) show higher RTN1 expression levels in colon tumors than common risk homozygous rs17094971AA subjects. This association is consistent with the minor rs17094983 A allele being inversely associated with CRC risk because reduction in the expression of RTN1 gene in patients carrying risk alleles would favor cell proliferation and survival of tumor colorectal cells. Further studies are required to conclusively assess the functional consequences of the rs17094983 polymorphism and its relevance in the susceptibility to the risk of family history of CRC.

Stratified analysis by histological lesions showed some additional differences in genotype distribution and allele frequencies between cases and controls. The most remarkable association was observed for the rs11255841T>A variant. Thus, individuals carrying the reported CRC risk rs11255841 allele A were significantly more frequent in FDRs of patients with CRC than that in controls among subjects with low-risk adenomas (dominant model, OR = 2.04; 95% CI: 1.19–3.51). The rs11255841T>A intergenic variant is located in the LINC00709 gene at the 10p14 chromosomal region. The LINC00709 gene belongs, such as LINC01500, to the new category of lncRNAs. Rather than to be transcriptional noise, recent studies suggest that lncRNAs are important players in cancer. It has been shown that lncRNAs regulate multiple functions in carcinogenesis including cell cycle, cell proliferation, and apoptosis through controlling gene transcription and posttranscriptional processing (28). Moreover, it has been observed that SNPs located in lncRNAs may influence gene expression through long-range cis-regulatory elements (29). In our population, the rs11255841T>A variant was in strong linkage disequilibrium (D’ = 0.96, r² = 0.84) with the rs10795668G>A SNP, previously identified as CRC risk factor by Tomlinson et al. (5). Functionally, both SNPs are located near to the DD431424 and HV455515 genes, which are important regulators of the hTERT region that harbor several susceptibility loci for various types of cancers, including CRC (30).

In our study, only 2 of the 88 SNPs analyzed were significantly associated with family history of CRC after False Discovery Rate test correction (rs17094983C>G > A in LINC01500, and rs11255841T>A in LINC00709). However, we consider that some SNPs (Table 2) merit additional follow-up evaluation for risk of family history of CRC because Q values were close to required significance levels. Taking into account the prevalence of the SNPs evaluated in our population, the study has a power of 85% to detect ORs > 1.41 or <0.73. As a result, it is possible that we could have missed minor statistical differences, mainly in low-frequency variant polymorphisms and stratified analysis. Studies with larger populations and different ethnic groups are warranted to elucidate the contribution of genetic susceptibility on the risk of family history of CRC.

In summary, we found that some polymorphisms previously related to CRC risk (rs17094983 and rs11255841) show significant differences in genotype distribution and allele frequencies between FDRs of patients with CRC and individuals with no family history of CRC. Of interest, the observed associations were in the same direction than those reported for CRC risk. Our results suggest that FDRs of CRC patients carry risk variants that would provide them a greater susceptible to developing the disease as compared to individuals with no family history of CRC. A deeper knowledge of genetic factors related to familiar CRC may have significant implications for the identification of those FDRs at risk of CRC that would benefit from stricter surveillance and cancer screening programs (Figure 2).

CONFLICTS OF INTEREST
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Specific author contributions: C.J.G.-P.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. A.L.: study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. P.C.-L.: statistical analysis. A.F.: study concept and design. E.Q., M.C., and I.A.-A.: acquisition of data. M.A.G.-G.: study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors approved the final draft submitted.

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Potential competing interests: None to report.

Study Highlights

**WHAT IS KNOWN**

- FDRs of patients with CRC have an increased risk of developing CRC and adenomas.
- GWAS studies have identified over 80 gene polymorphisms associated with CRC risk.
- The prevalence of CRC gene variants in FDRs of CRC patients as compared to individuals with no family history of CRC has been scarcely analyzed.

**WHAT IS NEW HERE**

- The protective rs17094983 variant (LINC01500) on the CRC risk was significantly less frequent in FDRs of CRC patients than that in individuals with no family history of CRC.
- The rs11255841 variant in the IncRNA LINC00709, associated with a higher CRC risk, was significantly more frequent in FDRs of patients with CRC among subjects with low-risk adenomas.
- The observed associations were in the same direction than those reported for CRC risk.

**TRANSLATIONAL IMPACT**

- FDRs of CRC patients have a higher probability of presenting a co-inheritance of multiple risk variants that would provide them a greater risk of developing CRC as compared to individuals with no family history of CRC.
- Genotyping of CRC risk variants in FDRs of CRC patients may have significant implications for the identification of those FDRs at risk that would benefit from stricter surveillance and CRC screening programs.
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