Polyadenylation Polymorphism in the Acetyltransferase 1 Gene (NAT1) Increases Risk of Colorectal Cancer

Douglas A. Bell, Elizabeth A. Stephens, Trisha Castranio, David M. Umbach, Mary Watson, Mark Deakin, James Elder, C. Hendrickse, Hamish Duncan, and Richard C. Strange

ABSTRACT

Exposure to carcinogens present in the diet, cigarette smoke, or the environment may be associated with increased risk of colorectal cancer. Aromatic amines (aryl- and heterocyclic) are a class of carcinogens that are important in these exposures. These compounds can be N- or O-acetylated by the NAT1 or NAT2 enzymes, resulting in activation or in some cases detoxification. Recent studies have shown that both NAT2 and NAT1 genes exhibit variation in human populations and that rapid acetylation by the NAT2 enzyme may be a risk factor for colorectal cancer. In this study we have analyzed for genetic polymorphism in both NAT1 and NAT2 in a group of 202 colorectal cancer patients and 112 control subjects from Staffordshire, England. We find significantly increased risk (odds ratio, 1.9; 95% confidence interval, 1.2-3.2; \( P = 0.009 \)) associated with the NAT1*10 allele of NAT1, an allele that contains a variant polyadenylation signal. Individuals with higher stage tumors (Duke's C) were more likely to inherit this variant allele (odds ratio, 2.5; 95% confidence interval, 1.3-4.7; \( P = 0.005 \)). In contrast, rapid acetylation genotypes of NAT2 were not a significant risk factor in this English population. However, we found that the risk associated with the NAT1 variant allele (NAT1*10) was most apparent among NAT2 rapid acetylators (odds ratio, 2.8; 95% confidence interval, 1.4-5.7; \( P = 0.003 \)), suggesting a possible gene-gene interaction between NAT1 and NAT2 (test for interaction; \( P = 0.12 \)). This is the first study to test for cancer risk associated with the NAT1 gene, and these positive findings suggest that NAT1 alleles may be important genetic determinants of colorectal cancer risk.

INTRODUCTION

Exposure to carcinogens in the diet, such as those found in well cooked or preserved meat, may be associated with increased risk of colorectal cancer (1). In addition, cigarette smoking has been associated with increased risk of colorectal cancer in several studies (1, 2). Aromatic amines (including arylamines and heterocyclic amines) are a group of carcinogenic compounds formed during combustion or pyrolysis of plant and animal protein (3, 4). Aromatic amines can also be formed via metabolic reduction of nitrogen oxide-substituted polycyclic aromatic hydrocarbons (5). These carcinogens are ubiquitous in the environment, in cooked food, and in smoke from cigarettes and other sources (3-5). Metabolism of these compounds is complex, with dozens of potential pathways, but acetylation is central to most activation or detoxification schemes for arylamines or heterocyclic amines. Acetylation of dietary mutagens, such as the heterocyclic amines Glu-P22 and MeIQ by the NAT1 or NAT2 gene products can lead to formation of reactive carcinogenic intermediates or to detoxification of these compounds depending on the context (6). N-acetylation activity varies widely in human populations as a result of sequence polymorphism at the NAT2 locus (7-11); thus, individuals with 2 nonfunctional alleles, "slow acetylators," have little or no NAT2 enzyme activity. The frequency of the NAT2 slow acetylator genotype varies between 5-90% worldwide (11-13). We recently developed a PCR-based technique for detection of the 5 most common NAT2 alleles, including a slow acetylator allele found only in individuals with African ancestry (11). Several studies have shown that the NAT1 enzyme can also acetylate aryl and heterocyclic amine carcinogens (6, 14), but less is known about the expression of NAT1 and its role in carcinogenesis. Interestingly, the NAT1 enzyme has frequently been referred to as the "monomorphic" acetyltransferase, relative to the "polymorphic" NAT2 N-acetyltransferase, but recent studies have revealed that there is considerable structural variation in the NAT1 gene (15) and that slow NAT1 phenotypes exist (16, 17). In particular, approximately 30% of populations with European ancestry carry a NAT1 allele (NAT1*10) with a variant polyadenylation signal in the 3'-untranslated region of the NAT1 mRNA (18). We hypothesized that the variant polyadenylation signal found in the NAT1*10 allele might alter polyadenylation of NAT1 mRNA and affect risk of colorectal cancer.

Several studies suggest that individuals with NAT2 rapid acetylation-phenotypes are at increased risk for cancer of the colon and that the etiological agent may possibly be exposure to carcinogenic heterocyclic amines found in cooked meat (18-21). However, no studies have tested the hypothesis that genetic variation in the NAT1 gene might be associated with increased risk for colon cancer. In this study we have analyzed a group of 202 colorectal cancer patients and 112 control subjects for genetic polymorphism in both NAT1 and NAT2. We find significantly increased risk for colorectal cancer associated with inheritance of an altered polyadenylation signal (NAT1*10) in the NAT1 gene.

MATERIALS AND METHODS

Subjects. All subjects were unrelated Caucasians and resident in the North Staffordshire area of England. The area is recognized as having a stable patient base with relatively little population movement. A sample (approximately 35% of incident cases) of patients with histologically proven adenocarcinoma of the colon or rectum was recruited in the North Staffordshire Hospital between 1990 and 1994. These patients represented approximately 35% of the incident cases seen in the clinical center. Among eligible patients asked to participate in the study, 100% of cases and 97% of controls were successfully enrolled.

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1 To whom requests for reprints should be addressed, at C3-03, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

2 The abbreviations used are: Glu-P22, 2-aminodipyrido-[l,2-a:3'2'íí]imidazole; MeIQ, 2-amino-3,4-dimethylimidazo[4,5-f]quinoline; NAT1, N-acetyltransferase 1 gene; NAT2, N-acetyltransferase 2 gene; CYP1A2, cytochrome P-450 1A2 gene; RFLP, restriction fragment length polymorphism; AS-PCR, allele-specific PCR; nt, nucleotide; OR, odds ratio; CI, confidence interval.
patients with inflammatory bowel disease. Data from cases were obtained by questionnaire at clinical interview and were limited to smoking (yes/no), family history of cancer, marital status, alcohol intake, drug intake, and occupation. Additional clinical data included previous surgery, tumor site, tumor stage and grade, histology and differentiation, and presence of inflammatory bowel disease. Data for colorectal cancer risk factors such as intake of fat, fiber, fruits, vegetables, red meat, drugs, and physical activity among study subjects were not available. The study was carried out with Ethics Committee approval and all participants gave informed consent. Statistical analysis was carried out with the use of the SigmaStat (Jandel Scientific, San Rafael, CA) and SAS software (SAS Systems, Cary, NC). Analysis of the association between smoking prevalence among cases (case-only analysis) and other variables was based on the assumption that these variables are independent (22). The gene-gene interaction hypothesis was assessed with the use of a logistic regression model that included a main effect for each gene and a gene-gene interaction term.

Acetyltransferase Genotype Analysis by PCR. DNA was extracted from 5 ml of peripheral blood lymphocytes by standard methods, resuspended in TE buffer (10 mM Tris, 1 mM EDTA), and frozen until used. For NAT2, the PCR-RFLP method was performed essentially as published (11). Briefly, a single PCR was carried out with the use of PCR primers (N5, 5’-gga aca aat tgg act tgg; N4, 5’-tct atg aat cac ttc gc) and aliquots of the PCR product were digested with restriction enzymes diagnostic for specific functional and nonfunctional alleles (WT, M1, M2, M3, and M4, corresponding to NAT2*4, NAT2*5A, NAT2*6A, NAT2*7A, and NAT2*14A). For an explanation of NAT gene nomenclature, see Vatsis et al. (23).

We genotyped the 4 published sequence variants in the 3’ region of NAT1 near the putative polyadenylation signal (see Fig. 1). The alleles detected were: (a) NAT1*4, the most common allele, which contains a consensus polyadenylation signal (nt 1086–1092); it has a “T” at nt 1088 and a “C” at nt 1095 (Refs. 18, 23); (b) NAT*3, a less common variant of allele NAT1*4, which has a “T” at nt 1088 and an “A” at nt 1095 (it also contains a consensus polyadenylation signal); (c) NAT1*10, which has an “A” at nt 1088, and “A” at nt 1095 (the change at nt 1088 results in a shift in the position of the mRNA polyadenylation signal (putative “rapid” allele)); and (d) NAT1*I1, which has a deletion of 9 nt in a trinucleotide repeat immediately upstream of nt 1088 (between nt 1066 and nt 1088 as indicated in Fig. 1). nt 1095 = “A”; it contains a consensus polyadenylation signal.

Several approaches were used to detect and confirm the existence of NAT1 polymorphisms. A PCR-RFLP method was used to distinguish between the NAT1*4, NAT1*10, and NAT1*I1 alleles. To differentiate the NAT1*10 allele from the NAT1*4 allele, the NAT1 reverse primer contained a mismatched base (T→G) at nt 1098 that created a partial MboII restriction site. Subsequent PCR amplification of the NAT1*4 allele with this primer resulted in a PCR product into fragments of 131, 71, and 45 bp. Digest of a NAT1*10 allele results in fragments of 131, 71, and 45 bp. The NAT1*I1 allele can be distinguished by observation of a 9-bp mobility shift of the 131-bp band to 122 bp (Lanes 5, 6, and 7). Lane 5, presence of a band at 131 bp due to poor MboII digestion of the NAT1*4/NAT1*10 heteroduplex PCR product. Heterozygotes produce the predicted composite patterns. Note the observation of a 9-bp mobility shift of the 122-bp band to 113 bp (Lanes 5, 6, and 7), respectively. MboII digestion of the NAT1*4 allele cut the PCR product into fragments of 105, 71, 45, and 26 bp. Digest of a NAT1*10 allele results in fragments of 131, 71, and 45 bp. The NAT1*I1 allele can be distinguished by observation of a 9-bp mobility shift of the 131-bp band to 122 bp (Lanes 5, 6, and 7). Lane 5, presence of a band at 131 bp due to poor MboII digestion of the NAT1*4/NAT1*10 heteroduplex PCR product. Heterozygotes produce the predicted composite patterns. Note that the RFLP method fails to distinguish between the NAT1*10 and NAT1*I1 alleles, b, AS-PCR discriminates between an “A” at nt 1088 (NAT1*10) and a “T” at nt 1088 (NAT1*I1 and NAT1*I4). The 268-bp band is β-globin. In the upper row of bands, the 223-bp band indicates the presence of the NAT1*4 allele. In the lower row of bands, the 223-bp band indicates the presence of the NAT1*10 allele. This approach cannot easily distinguish individuals with the NAT1*I1 allele (9-bp deletion).

To verify genotype assignments, we carried out direct sequencing of the PCR products with the Applied Biosystems Prism DyeDeoxy terminator sequenc-
ing kit and the ABI 373A DNA sequencer, following the manufacturer’s protocol (Applied Biosystems, Inc., Foster City, CA). We sequenced the NATI 3'-translated region for 40 individuals in this study who had a variety of genotypes (as well as ~80 individuals from other projects). We discovered that the NATI*3 allele exists (“A” at nt 1095 but “T” at nt 1088) and that ~3% of subjects carry this allele. The PCR-RFLP method misclassifies these individuals as NATI*10. We then developed an AS-PCR method to confirm the presence of NATI*10 alleles. This method used parallel PCRs for each DNA sample, with 5’ primer a1232 (5’-tac cag att gtt gtc cag ttc gg 3’) in combination with either primer V1 ak (5’-ggc atc tt aaa a g/t c atc tta) or primer V2 (5’-ggc atc tt aaa a t c atc tt) (20 pmol each). Conditions were the same as above, except that 2.5 mm MgCl2 was used in a volume of 30 μl, and the PCR was denatured at 94°C for 4 min and subjected to 30 cycles of 94°C for 30 s, 52°C for 30 s, and 72°C for 45 s. A final 72°C extension for 5 min was performed. Primers for β-globin (5 pmol) were added to this PCR to produce a 268-bp reference band in all AS-PCR reactions (as in Ref. 24). The PCR product from the NATI AS-PCR was 223 bp. Positive and negative controls were included in each set of PCR analyses. Results for this technique with the various genotypes are shown in Fig. 2b. The a priori hypothesis was that the NATI*10 allele was the “at-risk” allele. Our NATI genotype/phenotype comparisons suggest that the NATI*10 allele could be considered a “rapid” allele relative to the other alleles.3 In the data tables, NATI*2, NATI*4, and NATI*11 genotypes are arbitrarily labeled “slow.”

RESULTS

Colorectal case and control groups had similar frequency distributions for age and sex (cases: mean age, 63 years; male, 52%; female, 48%; controls: mean age, 63 years; male, 52%; female, 48%). Among colorectal patients, 33% were smokers at the time of diagnosis, but smoking status as an independent risk factor could not be assessed because this information was not available for the control population. However, among cases, smoking frequency was not associated with differences in tumor stage or grade. Data for other colorectal cancer risk factors was not available; therefore, adjustment for these factors was not conducted.

Table 1 displays calculated NATI allele frequencies for the groups in this study. Variant NATI allele frequencies (NATI*10 and NATI*11) in this English control group were similar to those observed in a European-American population sample from North Carolina.4 The allele frequency distribution among colorectal cancer patients differed from the control group. The NATI*4 and NATI*11 alleles were less frequent among cases, whereas the NATI*10 allele was more frequent among cases. Pooling the rare NATI*3 alleles with NATI*4 alleles, the overall allele frequency distributions among controls and cancers were significantly different (P = 0.03, 2 degrees of freedom).

Table 2 displays the frequencies of NATI genotypes among colorectal cancer cases and controls. The NATI*10 allele, containing the altered polyadenylation signal, was considered to be the a priori at risk allele.5 Genotypes containing the NATI*10 allele (heterozygotes and homozygotes) were more frequent among colorectal cancer cases (40 and 4%, respectively) compared to the control group (26 and 2.7%, respectively). There was a 1.8-fold risk associated with inheriting either of these genotypes. Genotypes including the NATI*11 allele were less frequent among cases (2.5%) relative to controls (6%), but this difference was not significant (OR, 0.6; P = 0.26). Table 2 also shows the risk calculation for the presumptive rapid genotypes relative to all presumptive slow genotypes (OR, 1.9; P = 0.009; any

3 Data from our laboratory indicate that the NATI*10 allele, containing the altered polyadenylation signal, is associated with higher tissue levels of NATI enzyme activity relative to the NATI*4 allele (D. A. Bell, A. Hirvonen, A. Badawi, N. P. Lang, K. Ilett, and F. F. Kadlubar. Polymorphism in the NATI polyadenylation signal: association of the NATI*10 allele with higher N-acetylation activity in bladder and colon tissue samples. Submitted for publication.). No data were available for the NATI*11 allele.

4 D. A. Bell, unpublished data.

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Table 1 Allele frequencies among the colorectal cancer and control populations for the 4 NATI alleles

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Colorectal cancer patients</th>
<th>Staffordshire control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NATI*10</td>
<td>0.72 (291)</td>
<td>0.77 (174)</td>
</tr>
<tr>
<td>NATI*9</td>
<td>0.02 (8)</td>
<td>0.03 (6)</td>
</tr>
<tr>
<td>NATI*10</td>
<td>0.24 (98)</td>
<td>0.16 (36)</td>
</tr>
<tr>
<td>NATI*11</td>
<td>0.017 (7)</td>
<td>0.045 (8)</td>
</tr>
</tbody>
</table>

* For nomenclature, see (Ref. 23); NATI*4, NATI*3, and NATI*11 are presumably “slow” alleles; NATI*10 is putatively a “rapid” allele.
* Four allele comparison, χ² = 3.33; P = 0.06; 3 df.
* Three allele comparison (NATI*4 and NATI*11 pooled), χ² = 7.0; P = 0.02; 2 df.

NATI*10 allele) and relative to NATI*11 containing genotypes (OR, 3.8; P = 0.023).

Tables 3 and 4 display the NATI and NAT2 genotype frequencies among the hospital-based controls and colorectal cancer cases. The frequency of genotypes containing the NATI*10 rapid allele increased from 29% among controls to 44% among cases (Table 3). Overall, individuals with an altered NATI polyadenylation signal (NATI*10 allele) had a 1.9-fold increased risk for colorectal cancer (95% CI, 1.2–3.1; P = 0.009). Following stratification of cases by tumor stage (Duke’s staging classification), the frequency of at risk NATI genotypes was increased among those with higher stage tumors relative to the control patients or to colorectal patients with lower stage tumors (Table 3). The frequency of NATI*10 genotypes was significantly higher among stage B (OR, 1.9; 95% CI, 1.1–3.4; P = 0.03) and stage C cases (OR, 2.5; 95% CI, 1.3–4.7; P = 0.006) but not among stage A cases when compared against the control population. This trend toward higher stage tumors among individuals with the NATI*10 genotypes was significant (Armitage-Doll trend test, P = 0.0015). Similarly, NATI*10 genotypes were more frequent among those with tumors that were graded as moderately or poorly differentiated (data not shown).

For NAT2 genotypes (Table 3), individuals with 2 nonfunctional alleles were classified as slow acetylators, whereas individuals with 1 or 2 functional alleles were classified as rapid acetylators (see Refs. 7–11). NAT2 rapid acetylator genotypes were slightly higher among cases compared to control subjects (OR = 1.1), but this difference was not significant. There was also a trend toward a higher frequency of NAT2 rapid acetylator genotypes among higher stage tumors, but this increase did not reach significance (P = 0.26). Slow acetylators were overrepresented among individuals with Duke’s A stage tumors, but there were very few cases in this group.

The frequencies of NATI rapid genotypes relative to tumor location were: ascending, 37% (22 of 59); transverse, 50% (4 of 8); descending, 51% (28 of 55); and rectal, 45% (29 of 65). NATI rapid genotypes were less frequent among those with a tumor in the ascending colon (37%); however, the lower frequency was not significantly different relative to other locations (P = 0.15). No significant differences in NAT2 genotype frequency were observed with regard to location of tumor. Among the 178 cases for whom we had smoking data (yes or no response), we tested for differences in genotype frequency between smokers and nonsmokers (case-only analysis, see Ref. 22). There was a higher frequency of NATI*10 genotypes among cases who were smokers (52%, 29 of 56) relative to nonsmoking cases (41%, 50 of 122), but this difference was not significant (OR, 1.5; 95% CI, 0.8–2.9; P = 0.19). Similarly, NAT2 rapid acetylator genotypes were slightly increased among smoking cases (52%) relative to nonsmoking cases (45%; OR, 1.3; 95% CI, 0.7–2.5; P = 0.4).

Table 5 shows the risk associated with combinations of NATI/NAT2 genotypes when the NATI slow/NAT2 slow genotypes
for colorectal cancer among all patients in this study (P = 0.009). Colorectal cancer patients with the NATI*10 allele were more likely to have an advanced stage tumor (Duke’s B or C). In addition, there appears to be a combined effect for NATI rapid genotypes and NAT2 rapid genotypes. Because we have no information about possible dietary or environmental intake of carcinogens (or other risk factors that could potentially confound these findings), this study cannot directly address the specific mechanism of risk for NATI in colon carcinogenesis. Indeed, there is still uncertainty regarding the strength of the associations between various dietary, or other, exposures and colorectal cancer (1, 2, 18-21). Although this limits our conclusions regarding the causal relation between NATI and colorectal cancer, we can offer a number of reasonable explanations.

Recent studies indicate that the NATI enzyme is expressed in colonic mucosa (25), indicating the potential for involvement in carcinogenesis. Indeed, there is still uncertainty regarding the strength of the associations between various dietary, or other, exposures and colorectal cancer (1, 2, 18-21). Although this limits our conclusions regarding the causal relation between NATI and colorectal cancer, we can offer a number of reasonable explanations.

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carcinogen metabolism in the colon. Our preliminary results suggest that NAT1*10 may lead to higher tissue levels of NAT1 enzyme, presumably by increasing NAT1 mRNA levels. Considering these data with the present finding of risk for the NAT1*10 allele, we suggest that the NAT1 enzyme may have an important role in the colon, possibly in activating carcinogens in the diet or in cigarette smoke. For example, NAT1-mediated O-acetylation of N-hydroxy compounds, or NAT1-mediated N/O-intramolecular acetyltransfer reactions may result in activation of some arylamines or heterocyclic amines; thus, high NAT1 activity could increase risk for some exposures. The higher frequency of NAT1*10 genotypes among smoking cases relative to nonsmoking cases (52 to 41%, respectively) suggests the possibility of an interaction between NAT1 and smoking exposure.

We also observed that NAT1*10 genotypes were more common among patients with higher stage tumors. Exposure to carcinogens has been associated with advanced stage in other cancer studies (26), and we suggest that the stage effect we observe may represent an interaction between NAT1 and exposure to carcinogens. That is, more advanced tumors have more genetic damage (27), and if this damage is, in part, caused by exposure to carcinogens, then NAT1 might be expected to have a greater effect in advanced stage tumors. In short, our observations in this study may be due to the NAT1 enzyme modulating the process of chemical carcinogenesis. Preliminary data from our laboratory indicate that the NAT1*10 allele also predisposes heavy smokers to develop bladder cancer (28). Thus, in the present study it may be that either dietary or smoking-related carcinogens contribute to the association between rapid NAT1 genotypes and higher stage tumors. We also have preliminary data suggesting that the NAT1*10 allele has a similar association with advanced stage gastric adenocarcinoma (29), a finding that would be consistent with a role for NAT1 in some common exposure-related etiologies for these two cancers.

In contrast to the significant association observed between NAT1 rapid genotypes and colorectal cancer, we detect no significantly increased risk associated with NAT2 rapid acetylation genotypes. It has been proposed that carcinogens formed in the broiling and frying of meat are metabolized through an N-hydroxylation step catalyzed by CYP1A2 that is followed by O-acetylation via acetyltransferases (either NAT1 or NAT2) (14, 20, 21, 30). This is believed to be an activation pathway for these compounds, and if so, the rapid acetylation genotype (NAT2) would be a risk factor among those that consume meats cooked by these methods (18–20). Several preliminary studies have been consistent with this hypothesis (18–20), although a more detailed follow-up study suggests that NAT2 rapid acetylation conveys significant risk only in combination with rapid oxidation phenotype (CYP1A2) and consumption of well cooked meat (21). In addition, a recent epidemiological study of colorectal adenoma by Probst-Hensch et al. (31) failed to detect a significant role for NAT2 genotype. In that study, as in the present study, data on cooking method preference were not collected. This suggests that one cannot detect a main effect for NAT2 genotype unless data on other effect modifiers are available or the prevalence of exposure to dietary carcinogens derived from well cooked meats is very high among the study participants.

It is interesting that the NAT1 gene effect was most apparent among those with the NAT2 rapid acetylator genotype (Table 5); unfortunately, a mechanistic basis for the potential interaction between these genes is far from clear. Some proposed pathways for activation of arylamines and heterocyclic amines involve both NAT1 and NAT2 enzymes (6, 14, 30), and the effect we observe with combined NAT1 and NAT2 rapid genotypes may be a hint that these pathways may be important in colorectal carcinogenesis. Because of the epidemiological limitations of this study, the finding that a NAT1 allele conveys significant risk in colon cancer must be considered preliminary. However, the result suggests several new hypotheses regarding the NAT1 gene, its role in carcinogen metabolism, and the etiology of colorectal cancer. We are carrying out further laboratory studies to characterize the molecular mechanism underlying the risk associated with NAT1 genotypes. Additional epidemiological studies of colorectal cancer and other exposure-related cancers are in progress, and we are hopeful that these studies will substantiate our finding that NAT1 alleles are important genetic determinants of colorectal cancer risk.

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