Genetic Variants of *UGT1A6* Influence Risk of Colorectal Adenoma Recurrence

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**Abstract**

**Purpose:** The UDP glucuronosyltransferase 1A6 (*UGT1A6*) and cytochrome P450 2C9 (*CYP2C9*) enzymes participate in the metabolism of nonsteroidal anti-inflammatory drugs, endogenous substances, and carcinogens. Functional polymorphisms of *UGT1A6* (T181A and R184S) and *CYP2C9* (R144C and I359L) have been reported to modify the protective effect of aspirin on colorectal adenoma risk. We aimed to further investigate the effect of these genetic variants on the development of colorectal neoplasia.

**Experimental Design:** We examined the relationship between *UGT1A6* and *CYP2C9* genotype and colorectal adenoma recurrence in 546 patients participating in a randomized placebo-controlled aspirin intervention trial.

**Results:** Although colorectal adenoma recurrence was not significantly influenced by *CYP2C9* genotype, carriers of variant *UGT1A6* alleles were at significantly reduced risk of colorectal neoplasia recurrence [relative risk (RR), 0.68; 95% confidence interval (95% CI), 0.52-0.89]. This risk reduction was also evident when the analysis was confined to advanced neoplasm recurrence (RR, 0.71; 95% CI, 0.47-1.09). When patients were stratified by genotype and aspirin intervention, those with variant *UGT1A6* alleles were at reduced recurrence risk irrespective of whether they received aspirin or placebo (RR, 0.62; 95% CI, 0.42-0.92 and RR, 0.63; 95% CI, 0.44-0.91, respectively).

**Conclusions:** These findings confirm that *UGT1A6* variants influence colorectal carcinogenesis independent of aspirin intake and suggest that they may have clinical value in secondary prevention programs for patients diagnosed with colorectal adenoma.

Regular aspirin or non-aspirin nonsteroidal anti-inflammatory drug (NSAID) consumption has been reported in many studies to reduce risk of developing colorectal neoplasia (1). Chemoprevention trials have also shown that aspirin reduces risk of colorectal adenoma recurrence (2, 3). Some studies of aspirin use and colorectal neoplasia risk have shown dose-dependent effects, with increasing aspirin dose resulting in greater clinical benefit (4, 5). Similarly, altered therapeutic effects may occur due to the wide variation in aspirin metabolism observed in humans (6).

The genes coding for enzymes involved in aspirin metabolism have polymorphic forms that have been shown to affect the expressed protein function; thus, interindividual pharmacokinetic differences in aspirin metabolism may be explained by inherited factors (7, 8). Aspirin is initially rapidly deacetylated to the active metabolite salicylic acid, which is further metabolized by glucuronidation and oxidation. The major enzymes involved in these reactions are, respectively, UDP glucuronosyltransferase 1A6 (*UGT1A6*) and cytochrome P450 2C9 (*CYP2C9*; refs. 7, 9). Two common variant *UGT1A6* alleles, *UGT1A6*+2 (T181A and R184S tandem mutation) and *UGT1A6*+4 (R184S single mutation), are associated with 30% to 50% reduced enzyme activity compared with wild type, whereas the *CYP2C9*+2 (R144C) and *CYP2C9*+3 (I359L) variant alleles result in 5% to 30% reduced enzyme activity (7, 8).

Interactions between aspirin use and *UGT1A6* and *CYP2C9* genotype have been reported in some case-control studies of colorectal adenoma risk, with the benefits of aspirin use being confined to carriers of slow-metabolism alleles (10, 11). Both enzymes, however, are also involved in the metabolism of a range of other substrates, including carcinogens. It is therefore conceivable that altered metabolism of non-NSAID substrates could also affect directly on colorectal carcinogenesis.
We sought to further investigate the role of UGT1A6 and CYP2C9 variants in colorectal neoplasia by genotyping patients participating in a randomized intervention trial of aspirin for the prevention of colorectal adenoma recurrence.

**Materials and Methods**

**Study participants.** The United Kingdom Colorectal Adenoma Prevention trial is a recently completed multicenter, randomized, placebo-controlled trial of aspirin and folate for the prevention of colorectal adenoma recurrence (12). Between 1997 and 2001, 945 patients were recruited to the trial. Eligible subjects had one or more histologically confirmed colorectal adenoma, ≥0.5 cm in size, detected at full colonoscopic examination, and were not already taking regular aspirin, non-aspirin NSAID, or folate supplements. Patients were randomized to aspirin alone (300 mg daily), folate alone (500 µg daily), both aspirin and folate, or double placebo. The primary end point was histologically confirmed recurrence of colorectal adenoma or colorectal carcinoma.

Recurrence was ascertained at follow-up colonoscopy scheduled for 3 years after entry colonoscopy, or done earlier if symptoms dictated. If follow-up colonoscopy was done before the 3-year time point, and colorectal adenoma or colorectal carcinoma was found then the patient left the trial, if no adenoma was found, then the patient continued on trial medication and underwent further colonoscopy at the 3-year time point. Histopathology was done at local hospitals without central review. Suspected recurrences found at follow-up colonoscopy were reviewed by the same histopathology department as the original trial entry specimen. Follow-up colonoscopy was done on 853 patients, and DNA for the molecular subprotocol was available from 546 patients, all of whom were of Caucasian ethnicity.

Information on lifestyle factors, including ethnicity and detailed family history data, was obtained from all study participants by dedicated interviewers during face-to-face interviews. Compliance with trial medication was assessed at 4-month intervals by research nurses during either telephone interviews or home visits. Patients were asked directly about compliance and potential side effects, and trial tablets were counted. At initial recruitment and follow-up visits, patients were asked to use acetaminophen for pain relief where necessary and to avoid the use of NSAIDs. In terms of compliance, 74% of patients continued in the aspirin arm (aspirin or aspirin placebo) until follow-up colonoscopy, and in >94% of these, there was ≥85% compliance with prescribed tablets.

Informed consent for the study was obtained from all participants, and the study was carried out with ethical review board approval in accordance with the tenets of the declaration of Helsinki.

**Genotyping.** Constitutional DNA was extracted from EDTA venous blood samples using a standard salt extraction procedure, and quantified by PicoGreen (Invitrogen, Paisley, United Kingdom). The UGT1A6*2, UGT1A6*4, CYP2C9*2, and CYP2C9*3 genotypes were generated using Taqman technology implemented on an ABI 7900HT sequence detection system (Applied Biosystems, Foster City, CA). Genotyping PCR reactions contained 6.25 µL ABI Taqman Master Mix, 0.16 µL ABI SNP assay-by-design master mix containing 900 nmol/L forward primer, 900 nmol/L reverse primer, 200 nmol/L VIC-labeled MGB probe and 200 nmol/L FAM-labeled MGB probe, 100 ng of template DNA, and double-distilled water to a final volume of 12.5 µL.

ABI Prism 7900 HT Sequence Detection System software, version 2.1 (Applied Biosystems) was used for Taqman genotyping analyses. Genotyping assays for each polymorphism were validated using control samples of known homozygote wild-type, heterozygote, and homozygote variant genotype generated by direct sequencing. Unblinded control samples were included on each sample plate and were correctly genotyped by the Sequence Detection System software on 100% of occasions. The positive call rate for unknown genotype samples was 99%. Samples that were called by the Sequence Detection System software were not repeated, whereas samples that were not called were genotyped using direct sequencing. Laboratory personnel employed in genotyping patient DNAs were blinded to clinical outcome. Details of all PCR primer sequences and reaction conditions are available upon request.

**Statistical analysis.** Baseline characteristics between the total United Kingdom Colorectal Adenoma Prevention trial population and the genotyped subgroup were compared using the χ² and t tests. Genotype frequencies were tested for departure from Hardy-Weinberg equilibrium using the χ² test. For each metabolism gene, patients homozygous wild type at both loci were compared with patients carrying one or two variant alleles at each locus and to individuals carrying any variant alleles. The presence or absence of colorectal neoplasia recurrence was considered a binary outcome in the cohort study. The relationship between genotype and risk of colorectal neoplasia recurrence was assessed by means of relative risks (RR) and 95% confidence intervals (95% CI) calculated using Poisson’s regression with robust error variances (13, 14). Both unadjusted and adjusted (for sex, age at trial entry, and interval between entry and follow-up colonoscopy) RR were calculated. Both models yielded similar results in all conditions; hence, only adjusted RR are presented.

The likelihood ratio test was used to explore interactions between genotype and aspirin treatment with respect to recurrence risk by comparing models with and without a multiplicative term for the two variables. For the interaction analyses, patients were divided into aspirin-treated (aspirin alone and aspirin and folate intervention groups) and non-aspirin-treated (folate alone and double placebo intervention groups) on an intention-to-treat basis.

Statistical analyses were undertaken using STATA, version 7.0 (Stata Corp., College Station, TX). All tests were two sided, and P < 0.05 was considered significant.

**Results**

There were no significant differences in age, sex, intervention group, interval between entry and follow-up colonoscopy, and outcomes between the total United Kingdom Colorectal Adenoma Prevention trial population and patients included in the genotyping analysis (Table 1). Of the 546 genotyped patients, 130 (23.8%) had one or more colorectal adenoma, and 7 (1.3%) had colorectal carcinoma detected at follow-up colonoscopy. Seventy patients (12.8%) had advanced colorectal neoplasia, defined as colorectal adenomas with villous or tubulovillous features, size ≥1 cm, severe dysplasia, or invasive carcinoma. In the main trial, a reduced colorectal adenoma recurrence risk was observed in patients who received aspirin (RR, 0.81; 95% CI, 0.65-1.02), and in the genotyped subgroup, a smaller recurrence risk reduction was also seen (RR, 0.92; 95% CI, 0.70-1.22). Folate did not influence recurrence risk (data not shown).

Allele frequencies for the UGT1A6*2 and UGT1A6*4 alleles were 32% and 1.5%, and for the CYP2C9*2 and CYP2C9*3 alleles were 12% and 7%, consistent with previous reports in Caucasian populations (10, 15). Genotype frequencies for the UGT1A6*2, UGT1A6*4, and CYP2C9*3 variants were in Hardy-Weinberg equilibrium (P = 0.41, P = 0.73, and P = 0.80 respectively), whereas genotype frequencies for the CYP2C9*2 variant showed some evidence of departure from Hardy-Weinberg equilibrium (P = 0.04).

Comparison with patients with homozygous wild-type genotype, patients with one or more variant UGT1A6 alleles had a significantly reduced risk of any colorectal neoplasia recurrence (RR, 0.68; 95% CI, 0.52-0.89; Table 2). When only
Table 1. Comparison of the total UKCAP trial population and patients genotyped in this study

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<tr>
<th>Variable</th>
<th>UKCAP trial population</th>
<th>Genotyped patients</th>
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<tr>
<td>n</td>
<td>853</td>
<td>546</td>
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<tr>
<td>Age* (y)</td>
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<tr>
<td>Mean</td>
<td>57.5</td>
<td>57.3</td>
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<tr>
<td>SD</td>
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<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>477 (56%)</td>
<td>289 (53%)</td>
</tr>
<tr>
<td>Female</td>
<td>376 (44%)</td>
<td>256 (47%)</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>217 (25.4%)</td>
<td>131 (24.0%)</td>
</tr>
<tr>
<td>Folate alone</td>
<td>215 (25.2%)</td>
<td>144 (26.4%)</td>
</tr>
<tr>
<td>Aspirin and folate</td>
<td>217 (25.4%)</td>
<td>135 (24.7%)</td>
</tr>
<tr>
<td>Double placebo</td>
<td>204 (23.9%)</td>
<td>136 (24.9%)</td>
</tr>
<tr>
<td>Colonoscopy interval(1) (mo)</td>
<td>40.3</td>
<td>40.7</td>
</tr>
<tr>
<td>Mean</td>
<td>40.3</td>
<td>40.7</td>
</tr>
<tr>
<td>Range</td>
<td>2-79</td>
<td>6-74</td>
</tr>
<tr>
<td>Outcome(1)</td>
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<tr>
<td>Adenoma</td>
<td>207 (24.2%)</td>
<td>130 (23.8%)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>11 (1.3%)</td>
<td>7 (1.3%)</td>
</tr>
<tr>
<td>Advanced neoplasia</td>
<td>104 (12.2%)</td>
<td>70 (12.8%)</td>
</tr>
</tbody>
</table>

Abbreviation: UKCAP, United Kingdom Colorectal Adenoma Prevention.

*Age at entry colonoscopy.
\(1\) Interval between entry and follow-up colonoscopy.

Discussion

We hypothesized that genetic variants with functional relevance in aspirin metabolism might alter the effectiveness of aspirin in preventing colorectal adenoma recurrence. Intriguingly, the results from this controlled trial indicate that individuals with one or more variant UGT1A6 alleles are at significantly reduced recurrence risk regardless of aspirin treatment. Furthermore, the risk reduction associated with variant UGT1A6 alleles persisted when the analysis was restricted to detection of advanced lesions, which are of greater clinical significance.

Evidence from case-control studies investigating the combined effects of aspirin and UGT1A6 genotype in determining colorectal neoplasia risk is inconsistent. Two case-control studies of colorectal adenoma risk have reported a significant interaction (10, 11). However, the first study did not observe a similar interaction for non-aspirin NSAIDs, which are also metabolized by UGT1A6, and the second study did not consider non-aspirin NSAID use. In addition, a recent study of colorectal carcinoma risk did not document an interaction between either aspirin or non-aspirin NSAID and UGT1A6 genotype (15). In case-control studies, a relatively low frequency of aspirin intake (usually one to two tablets per week) is considered to indicate exposure, and typically, 20% to 30% of participants report this level of drug use. In our study, half of the participants were randomized to aspirin intervention, and drug exposure was comparatively high, thus increasing the likelihood of detecting an interaction. It is also possible, however, that the median 43-month treatment duration in our study was insufficient to observe any putative gene-environment interactions.

Unlike other UGT1 enzymes, which are mainly expressed in the liver, UGT1A6 is widely expressed in extrahepatic tissues, including the colon, and induction of UGT1A6 has been shown in human colon adenocarcinoma Caco-2 cells (16, 17). The UGT1A6 enzyme catalyzes glucuronidation of a range of other substrates apart from aspirin, including carcinogens, such as benzo(a)pyrene, 2-naphthylamine, and 4-aminobiphenyl (18). Comparisons of UGT1A6 glucuronidation rates indicate that acetylsalicylic acid (aspirin), salicylic acid, and other NSAIDs are in fact relatively poor substrates; therefore, changes in enzyme activity due to variant alleles will have greater effect on metabolism of other substrates (7). Thus, altered metabolism of any one or combination of UGT1A6 substrates other than aspirin could underlie the reduced colorectal adenoma recurrence seen in our study.

Initial in vitro enzyme kinetic analysis reported a 25% to 75% reduced glucuronidation with the UGT1A6*2 allele compared with wild type, depending on the substrate and reaction conditions (7). Subsequently, however, two studies have reported higher enzyme substrate affinity and activity for the UGT1A6*2 alloenzyme in human embryonic kidney cells and tumor tissue from colorectal cancer hepatic metastases (19, 20). In these studies, increased enzyme activity with the UGT1A6*2 allele was shown across a range of substrates, although salicylic acid was not specifically tested. Alloenzymes with the R184S variant (either alone or in tandem with T181A) resulted in increased substrate affinity compared with the wild type. This polymorphism maps to a hypervariable region in the NH2-terminal half of the UGT1A6 protein and may be important in advanced colorectal neoplasia recurrence was considered, a similar risk reduction for carriers of variant UGT1A6 alleles was observed (RR, 0.71; 95% CI, 0.47-1.09). In contrast, patients with one or more variant CYP2C9 alleles were not at significantly altered risk of either any or advanced colorectal neoplasia.

Risks of any colorectal neoplasia recurrence after stratification for both genotype and aspirin treatment are detailed in Table 3. When compared with patients with wild-type UGT1A6 genotype who did not receive aspirin, patients with variant UGT1A6 genotype had a significantly reduced recurrence risk regardless of aspirin treatment (RR, 0.63; 95% CI, 0.44-0.91 for non-aspirin treated; RR, 0.62; 95% CI, 0.42-0.92 for aspirin treated). There was no significant interaction between UGT1A6 genotype and aspirin treatment (\(P = 0.7\)). Again, a similar pattern of risk was observed when only advanced colorectal neoplasia was considered (Table 4). Patients with variant UGT1A6 genotype treated with either non-aspirin or aspirin had a reduced advanced neoplasia recurrence risk when compared with those with wild-type genotype who received non-aspirin (RR, 0.57; 95% CI, 0.33-0.96 and RR, 0.59; 95% CI, 0.34-1.05, respectively). There was also no interaction between UGT1A6 genotype and aspirin treatment when advanced neoplasia recurrence was considered.

After stratification by CYP2C9 genotype and aspirin treatment, no significant alterations in risk of either any or advanced colorectal neoplasia recurrence were observed, and there were no significant interactions.

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After stratification by CYP2C9 genotype and aspirin treatment, no significant alterations in risk of either any or advanced colorectal neoplasia recurrence were observed, and there were no significant interactions.
defining substrate specificity. If this in vitro data on enzyme activity are mirrored in vivo, then carriers of variant alleles would be expected to metabolize aspirin more rapidly and thus show a reduction in the protective effects of aspirin in prevention of colorectal neoplasia. This is the opposing interaction to that reported in some case-control studies. Furthermore, although aspirin metabolism in man is highly variable, glucuronidation products formed by UGT1A6 account for only 1% to 50% (mean = 13%) of aspirin metabolites (6). Collectively, these data are consistent with a model in which the main effect of UGT1A6 genotype seen in this study is due to altered metabolism of a substrate other than aspirin. Increased metabolism of carcinogens due to variant UGT1A6 alleles would be expected to reduce recurrence risk in exposed subjects, and this may account for the reduced risk in carriers of UGT1A6 variants observed in this study.

In our study, the CYP2C9 genotype did not influence colorectal adenoma recurrence or interact with aspirin treatment. Previous case-control studies of both colorectal adenoma and colorectal carcinoma risk have also observed no significant interaction between CYP2C9 genotype and aspirin or non-aspirin NSAID use (15, 21). Only 3% of salicylic acid metabolism occurs through oxidation by CYP2C9; however, this enzyme plays a greater role in the metabolism of NSAIDs, in particular diclofenac, and thus, CYP2C9 genetic variants may have a greater influence on the effects of these drugs (22).

### Table 2. Risk of detection of any colorectal neoplasia and advanced neoplasia at follow-up colonoscopy according to UGT1A6 and CYP2C9 genotypes

| Gene | Genotype | Any colorectal neoplasia | | | | Advanced colorectal neoplasia* | | |
| --- | --- | --- | --- | | | | | | |
| | | Detected/not detected | RR* (95% CI) | | | Detected/not detected | RR* (95% CI) | | |
| UGT1A6 | *1*1*1 | 75/168 | Reference | | | 38/205 | Reference | | |
| | *1*2 | 50/186 | 0.70 (0.52-0.93)* | | | 27/209 | 0.77 (0.50-1.19) | | |
| | *2*2 | 10/41 | 0.63 (0.36-1.09) | | | 3/48 | 0.38 (0.12-1.17) | | |
| | *2*4 | 2/7 | 0.91 (0.31-2.65) | | | 2/7 | 1.87 (0.63-5.48) | | |
| | *1*4 | 0/7 | Reference | | | 0/7 | Reference | | |
| | Any variant allele | 62/241 | 0.68 (0.52-0.89)* | | | 32/271 | 0.71 (0.47-1.09) | | |
| CYP2C9 | *1*1*1 | 84/273 | Reference | | | 43/314 | Reference | | |
| | *1*2 | 35/81 | 1.19 (0.87-1.64) | | | 15/101 | 0.98 (0.56-1.71) | | |
| | *2*2 | 13/44 | 0.94 (0.59-1.49) | | | 9/48 | 1.29 (0.69-2.41) | | |
| | *2*3 | 2/0 | Reference | | | 0/2 | Reference | | |
| | Any variant allele | 53/136 | 1.09 (0.82-1.44) | | | 27/162 | 1.07 (0.68-1.67) | | |

*Advanced colorectal neoplasia was defined as colorectal adenomas with villous or tubulovillous features, size ≥1 cm, severe dysplasia, or invasive carcinoma.

1 RR and 95% CI adjusted for age, sex, and interval between entry and follow-up colonoscopy.

*1, wild-type allele.

*P = 0.02.

*P = 0.005.

**Patients with one or two UGT1A6*2 or UGT1A6*4 alleles.

**Patients with one or two CYP2C9*2 or CYP2C9*3 alleles.

### Table 3. Risk of detection of any colorectal neoplasia by genotype and aspirin treatment

| Gene | Genotype | Non-aspirin treated | | | | Aspirin treated | | |
| --- | --- | Colorectal neoplasia detected/not detected | RR* (95% CI) | | | Colorectal neoplasia detected/not detected | RR* (95% CI) | | |
| UGT1A6 | *1*1*1 | 41/83 | Reference | | | 34/85 | 0.88 (0.62-1.26) | | |
| | Variant | 33/123 | 0.63 (0.44-0.91)* | | | 29/118 | 0.62 (0.42-0.92)* | | |
| CYP2C9 | *1*1*1 | 45/137 | Reference | | | 39/136 | 0.94 (0.65-1.35) | | |
| | Variant | 29/69 | 1.06 (0.72-1.57) | | | 24/67 | 0.95 (0.64-1.42) | | |

*RR and 95% CI adjusted for age, sex, and interval between entry and follow-up colonoscopy.

*1*1 genotype includes patients with two *1 (wild type) alleles; variant genotype includes patients with one or two UGT1A6*2 or UGT1A6*4 alleles.

*P = 0.01.

*P = 0.02.

*1*1 genotype includes patients with two *1 (wild type) alleles; variant genotype includes patients with one or two CYP2C9*2 or CYP2C9*3 alleles.
In summary, our study is the first to investigate the effects of UGT1A6 and CYP2C9 variants on colorectal neoplasia recurrence in the context of a controlled trial. Patients with variant UGT1A6 genotypes had a significantly reduced risk of recurrence irrespective of aspirin treatment. The observation of a relationship between UGT1A6 genotype and colorectal adenoma risk suggests that variation in this enzyme influences colorectal adenoma development and may have clinical use in the design of secondary prevention programs for patients diagnosed with colorectal adenoma.

### References

17. Munzel PA, Schmohl S, Heel H, Kalberer K, Bock-Hennig BS, Bock KW. Induction of human UDP-glucuronosyltransferases (UGT1A6, UGT1A9, and UGT2B7) by t-butylhydroquinone and 2,3,7,8-tetrachlorodibenzo-p-dioxin in Caco-2 cells. Drug Metab Dispos 1999;27:569–73.
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