Short Communication

GSTM1, GSTT1, and GSTP1 Polymorphisms and Risk of Advanced Colorectal Adenoma

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Abstract

Cigarette smoking is a risk factor for colon adenoma. The glutathione S-transferase enzymes are involved in the detoxification of carcinogenic compounds including those found in tobacco smoke, and thus, may be important modifiers of individual risk of developing this disease. We examined the prevalence of GSTM1 and GSTT1 gene deletions, and two GSTP1 polymorphisms in 772 cases with advanced colorectal adenomas (>1 cm, villous elements or high-grade dysplasia) of the distal colon (descending or sigmoid colon or rectum) and 777 sigmoidoscopy negative controls enrolled in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Epidemiologic data on smoking was collected by self-administered questionnaire and DNA was extracted from whole blood or buffy coat. For GSTM1 and GSTT1, we used a newly developed TaqMan-based assay capable of discriminating heterozygous (+/-) individuals from those with two active alleles (+/+ ) and homozygous deletions (–/–). For GSTP1, the I105V and the A114V substitutions were identified using end point 5’ nuclease assays (TaqMan). Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were determined using unconditional logistic regression, controlling for age, race, and gender. Advanced adenoma risk was increased in current/former smokers (OR, 1.4; 95% CI, 1.2-1.8). Risks were decreased in subjects with ≥1 inactive GSTM1 alleles (OR, 0.6; 95% CI, 0.4-0.9); and the association was independent of smoking status (P interaction = 0.59). Having ≥1 inactive GSTT1 allele was associated with increased risk among smokers (OR, 1.4; 95% CI, 1.1-1.9; P trend = 0.02) but not among never smokers (OR, 0.9; 95% CI, 0.6-1.3) and a significant interaction between smoking and genotype was observed (P interaction = 0.05). In summary, this is the first study to report associations between colorectal adenomas and GSTM1 wild-type and GSTT1 null allele among smokers. These findings only became apparent using a newly developed assay able to distinguish heterozygous from wild-type individuals. Our data provide evidence that phenotypic differences between these two groups exist. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1823–7)

Introduction

Colorectal adenoma is a recognized precursor of colorectal cancer based on epidemiologic, histologic, and genetic studies demonstrating shared genetic alterations (1, 2). Tobacco smoking is an established risk factor for colorectal adenoma and cigarette smoking is an important component of the carcinogenic effect of cigarette smoke. Tobacco smoke is a rich source of glutathione S-transferase enzymes are involved in the detoxification of carcinogenic compounds including those found in tobacco smoke, and thus, may be important modifiers of individual risk of developing this disease. We examined the prevalence of GSTM1 and GSTT1 gene deletions, and two GSTP1 polymorphisms in 772 cases with advanced colorectal adenomas (>1 cm, villous elements or high-grade dysplasia) of the distal colon (descending or sigmoid colon or rectum) and 777 sigmoidoscopy negative controls enrolled in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Epidemiologic data on smoking was collected by self-administered questionnaire and DNA was extracted from whole blood or buffy coat. For GSTM1 and GSTT1, we used a newly developed TaqMan-based assay capable of discriminating heterozygous (+/-) individuals from those with two active alleles (+/+ ) and homozygous deletions (–/–). For GSTP1, the I105V and the A114V substitutions were identified using end point 5’ nuclease assays (TaqMan). Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were determined using unconditional logistic regression, controlling for age, race, and gender. Advanced adenoma risk was increased in current/former smokers (OR, 1.4; 95% CI, 1.2-1.8). Risks were decreased in subjects with ≥1 inactive GSTM1 alleles (OR, 0.6; 95% CI, 0.4-0.9); and the association was independent of smoking status (P interaction = 0.59). Having ≥1 inactive GSTT1 allele was associated with increased risk among smokers (OR, 1.4; 95% CI, 1.1-1.9; P trend = 0.02) but not among never smokers (OR, 0.9; 95% CI, 0.6-1.3) and a significant interaction between smoking and genotype was observed (P interaction = 0.05). In summary, this is the first study to report associations between colorectal adenomas and GSTM1 wild-type and GSTT1 null allele among smokers. These findings only became apparent using a newly developed assay able to distinguish heterozygous from wild-type individuals. Our data provide evidence that phenotypic differences between these two groups exist. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1823–7)

Materials and Methods

The Prostate, Lung, Colorectal, and Ovarian Cancer Trial. This trial, which is being carried out by the National Cancer Institute, has randomized 77,465 screening arm participants (38,350 men and 39,115 women) and an equal number of nonscreened controls, ages 55 to 74, at 10 screening centers throughout the U.S. (12, 13).
Study Population. Cases and controls for this study were drawn from the screening arm participants at the 10 screening centers of the Prostate, Lung, Colorectal, and Ovarian Cancer Trial who filled out a risk factor questionnaire, had a successful sigmoidoscopy (insertion to at least 50 cm with >90% of mucosa visible or a suspect lesion identified), and provided a blood sample for use in etiologic studies (September 1993-September 1999, applied conditions described; n = 42,837; ref 14). Of these participants, we excluded 4,834 with a self-reported history of ulcerative colitis, Crohn’s disease, familial polyposis, colorectal polyposis (Gardner’s syndrome, or Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or cutaneous basal cell skin cancer). We randomly selected 772 of 1,234 cases with at least one advanced colorectal adenoma (adenoma ≥1cm or containing high-grade dysplasia or villous, including tubulovillous elements) in the distal colon (descending colon and sigmoid or rectum), and 777 or 26,651 control participants with a negative sigmoidoscopy screening (ie, no polyp or other suspect lesion), frequency-matched to the cases by gender and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and others). Study subjects were predominantly non-Hispanic Whites (94%). Among the 772 cases, 572 (74%) had a lesion ≥1cm, 489 (63%) showed advanced histologic features, and 245 (32%) had multiple adenoma. Also, 631 (82%) cases had an advanced adenoma of the descending colon or sigmoid and 232 (30%) had an advanced adenoma of the rectum, including subjects having lesions at both sites. Questionnaire data and blood collection were previously reported (15). For risk evaluation related to recent smoking, smokers were categorized as long-term quitters (quit ≥10 years before enrollment) and current or recent smokers (quit <10 years before enrollment). Because risks associated with polymorphic variants were similar for both former and current and recent smokers, they were combined as ever smokers to increase power in this group. Dietary nutrient intake was calculated by multiplying the reported frequency of consumption for relevant food items by gender- and nutrient-specific portion sizes (16), using the nutrient database from the U.S. Department of Agriculture (17). Dietary intake including intake of benzo(a)pyrene, heterocyclic amines [PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine), and MeIQx (2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline)] were estimated using data from the CHARRED database (http://charred.cancer.gov).

GSTM1, GSTT1, and GSTP1 Genotype Assays. A new method was developed at the National Cancer Institutes Core Genotyping Facility to distinguish heterozygotes from subjects with two active GSTM1 and T1 alleles. The method used TaqMan real-time PCR technology with two 5’ nuclease probes and four PCR primers (http://snp500cancer.nci.nih.gov/assays/). Because GSTT1 and GSTM1 are members of a multigene family, we chose to compare the members of the same class to ensure a gene-specific assay design. All sequences used in assay design were obtained from Genbank: GSTM1, NM_000561; GSTM2, NM_000848; GSTM3, NM_000849; GSTM5, NM_000851, and GSTT1, NM_000853; GSTT2, NM_000854f. Gene-specific primers and probes (http://snp500cancer.nci.nih.gov/assays/) were selected for specificity to one gene target and subsequently checked using Primer3 software (18).

Assays were independently done using 10 μg of lyophilized genomic DNA in a 5 μL TaqMan reaction. Reactions were done in a 384-well plate (96 x 4) format. Three controls with known gene copy numbers (Coriell DNA controls) as well as no-template controls were analyzed alongside samples. We designed two assay sets for the GSTM1 genotype assay and two assay sets for the GSTT1 genotype assay. Each assay set contained two PCR primers and one dual labeled probe. The corresponding assay sets for the human genomic region in IVS 10 of the BRCA1 gene as a two-copy gene control. The test assay sets were designed to hybridize within a commonly deleted area of the inactive genetic variant making it possible to quantify the active allele copy number by the rate of amplification. The GSTM1 and GSTT1 real-time assays were conducted using 2.5 μL of the 2× Universal Master Mix (ABI, Foster City, CA). Specific primers and probes used in the reaction are presented on the National Cancer Institute’s Core Genome Facility web site (http://snp500cancer.nci.nih.gov/assays/). Thermocycling conditions were: 95°C for 2 minutes, 95°C for 10 minutes, followed by 49 cycles 95°C for 30 seconds, and 60°C for 1 minute. Real-time fluorescence was monitored during PCR amplification and results analyzed using methods similar to Covault et al. (19). Assay validation, optimization, and genotype prevalence was conducted using Coriell samples from 102 individuals of four ethnicities. This information is available on the National Cancer Institute’s SNP500 database web page at http://snp500cancer.nci.nih.gov/ (20).

Two single nucleotide polymorphisms at the GSTP1 locus were genotyped using the end point 5’ nuclease TaqMan assay. Specific primers, probes, and methods used to detect polymorphisms at codons 105 and 114 are also publically available at http://snp500cancer.nci.nih.gov/ (20). All TaqMan output was processed electronically for downloading into analytical programs.

Coriell DNA samples containing the homozygous major and minor allele and heterozygotes served as internal laboratory quality controls for each polymorphism studied. Four of each control type and four no-template controls were included per plate. External blinded samples from 40 individuals were interdispersed throughout analyses. The blinded samples showed 100% interassay concordance for all assays.

Genotype data were successfully obtained for 89% to 91% of study subjects, excluding those with insufficient DNA (～6%), genotyping failures (3.5%), and those whose fingerprint profiles showed subject-specific ambiguities (<1%).

Statistical Analysis. Adenoma risk was estimated by calculating odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression (Stata 8.1, College Station, TX). Analyses were adjusted for gender, race (non-Hispanic White, non-Hispanic Black, others), age at entry (55-59, 60-64, 65-69, 70-74), and when not used as a stratifying factor, smoking status (never, ever smoker). Adjustments for other suspected confounders, including education, history of colorectal cancer in a first-degree relative, body mass index, and dietary red meat intake were not included in the model because they did not alter the OR by 10% and/or did not have a P value ≤0.1 in the multivariate model. Associations between broccoli consumption was analyzed by dividing cases and controls above and below the median intake of broccoli (g/d), and also by quartiles (Q1, 0-3.59; Q2, >3.59-9.06; Q3, >9.06-15.60; Q4, >15.60). Subjects who reported never eating broccoli were also used as a comparison group. Dietary analyses included adjustment for exercise and fiber intake in addition to factors listed above (age, sex category, and race). Tests for interaction were conducted using a likelihood ratio test.

Based on a novel extension of polytomous logistic regression for multivariate outcome analysis (21), we studied whether the prevalence of glutathione S-transferase alleles varied for three characteristics of adenomas: size (≥1 versus <1 cm), multiplicity (multiple versus single), and advanced histologic features (high-grade dysplasia or villous structure versus absence of these features), estimating case-case ORs for each characteristic after controlling for the other two characteristics. All P values were two-sided. Individuals with missing values were excluded from specific analyses.

Results

Distributions between cases and controls were essentially the same for matching factors, gender, and race. However, cases tended to be older, more likely to report a first-degree family history of colorectal cancer, have less education, and a higher body mass index at study entry (Table 1).
Cigarette smoking was associated with advanced adenoma, with greater risks for current smokers and recent smokers who quit <10 years ago (OR, 2.4; 95% CI, 1.8-3.1) than for former smokers who quit >10 years ago (OR, 1.1; 95% CI, 0.9-1.4; \( P_{\text{trend}} < 0.001 \); Table 2).

Also in Table 2, genotype distributions are presented for cases and controls. A lower risk of colorectal adenoma was observed among those carrying \( \geq 1 \) null GSTM1 allele (\(-/-\) and \(+/-\)) when compared with individuals carrying two active alleles (+/+) (OR, 0.6; 95% CI, 0.4-0.9). Lower relative risks were not observed when heterozygotes were grouped with those carrying two active alleles as would have been observed by PCR fragment analysis (OR, 0.9; 95% CI, 0.8-1.2, data not shown). Neither the GSTT1 nor GSTP1 variants were associated with adenoma risk. By multivariate disease characteristic analysis (21), only the GSTP1 GG genotype at codon 105 was associated with large adenomas (>1 cm) compared with small adenomas (OR, 0.5; 95% CI, 0.2-1.2) compared with GSTM1 (+/+) individuals with low consumption of broccoli (<9.1g/d). For the GSTT1 gene, individuals with \( \geq 1 \) null allele continued to be at lower risk regardless of broccoli intake. Increased risks were only associated with the GSTT1 (\(-/-\)) polymorphism in the high broccoli consumption group (OR, 1.7; 95% CI, 1.1-2.7) compared with GSTT1 (+/+ in the low broccoli consumption group. The same results were obtained when individuals who never consumed broccoli were used as a comparison group. Risks associated with genetic variants were not modified by dietary red meat or estimated dietary benzo(a)pyrene, PhIP, or MeIQx intake when all subjects or only subjects who had never smoked were considered (data not shown).

### Discussion

This investigation of glutathione S-transferase polymorphisms and advanced adenoma risk revealed reduced risks in carriers of \( \geq 1 \) GSTM1 null allele, however, this association was not related to tobacco use or other factors examined. If this result were seen only among subjects who consumed higher amounts of broccoli, this finding could have been explained by isothiocyanate-induced protection, however, this was not what we observed. These findings remain puzzling, as they could have been caused by small numbers in the homozygous active (+/+ group, and should be confirmed. Excess risks associated with carriage of \( \geq 1 \) GSTT1 null allele were only observed among smokers. Both of these findings would not have been observed by the method of PCR fragment analysis on gel electrophoresis. The two single nucleotide polymorphisms associated with amino acid substitutions at codons 105 and 114 of the GSTT1 gene did not contribute to overall adenoma risk in this study, however, the GG genotype at codon 105 was significantly associated with adenoma size. GSTM1 and GSTT1 have been widely studied in relation to colorectal cancer because of their high expression in the...
gastrointestinal tract and their role in detoxification of food- and tobacco-derived carcinogens. Studies have not generally found significant associations (22-25). We observed associations for GSTM1 and GSTT1 with adenoma risk only when +/− and ++ individuals were analyzed separately. Our data provide supportive evidence that phenotypic differences between ++ and +/− individuals exist. As in previous studies, our findings would have been negative had subjects with ≥1 active alleles been combined.

Although genotype-phenotype concordances have been shown with the PCR fragment analysis approach for GSTM1 and GSTT1, it is unclear whether a gene dosage effect exists (26-29). Experimental studies suggested a bimodal distribution of ex vivo GSTM1 overall (26); however, the authors also reported that ~20% of the subjects were considered “very highly active.” Similar studies of GSTT1 (27-29) enzymatic activity were clearly trimodal, however, additional experimental studies employing genotyping approaches that categorize allele count are needed to more precisely specify these relationships.

The results of this study do not support a relationship between GSTP1 polymorphisms and adenoma risk. We also found no evidence for a modifying effect of glutathione S-transferase genotype on the association between adenoma

### Table 2. Risk of left-sided advanced colorectal adenoma, by smoking history, broccoli intake, and genotype

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Controls (n = 777)</th>
<th>Cases (n = 772)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>315 (40.8)</td>
<td>260 (33.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Former, quit ≥10 y</td>
<td>302 (39.2)</td>
<td>272 (35.4)</td>
<td>1.1 (0.9-1.4)</td>
</tr>
<tr>
<td>Current and recent quitters (&lt;10 y)</td>
<td>111 (14.4)</td>
<td>198 (25.8)</td>
<td>2.4 (1.8-3.1)</td>
</tr>
<tr>
<td>P&lt;sub&gt;trend&lt;/sub&gt;*</td>
<td>&lt;0.001</td>
<td>2.4 (1.8-3.1)</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>419 (57.1)</td>
<td>473 (64.5)</td>
<td>1.4 (1.2-1.8)</td>
</tr>
<tr>
<td>Cigar/pipe</td>
<td>43 (5.6)</td>
<td>39 (5.1)</td>
<td>1.2 (0.7-1.9)</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, and gender.

1Smoking pipe and cigar and former smokers combined were not included in the trends estimation.

### Table 3. Risk of left-sided advanced colorectal adenoma associated with cigarette smoking, and specific GSTM1, GSTT1, and GSTP1 polymorphisms

<table>
<thead>
<tr>
<th></th>
<th>Never smokers</th>
<th></th>
<th></th>
<th></th>
<th>Ever smokers</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls n (%)</td>
<td>Cases n (%)</td>
<td>OR (95% CI)*</td>
<td></td>
<td>Controls n (%)</td>
<td>Cases n (%)</td>
<td>OR (95% CI)*</td>
<td>P interaction</td>
</tr>
<tr>
<td>GSTM1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>+/+</td>
<td>12 (4.4)</td>
<td>18 (8.1)</td>
<td>1.0 (reference)</td>
<td></td>
<td>23 (6.1)</td>
<td>40 (9.8)</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>110 (40.4)</td>
<td>87 (39.6)</td>
<td>0.5 (0.2-1.2)</td>
<td>150 (39.7)</td>
<td>150 (36.9)</td>
<td>0.6 (0.3-1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>++</td>
<td>150 (55.2)</td>
<td>115 (52.3)</td>
<td>0.5 (0.2-1.1)</td>
<td>205 (54.2)</td>
<td>217 (53.5)</td>
<td>0.6 (0.3-1.0)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;trend&lt;/sub&gt; = 0.2</td>
<td></td>
<td></td>
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<td></td>
<td>P&lt;sub&gt;trend&lt;/sub&gt; = 0.1</td>
<td></td>
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<tr>
<td>+/- and --/-</td>
<td>260 (95.6)</td>
<td>202 (91.9)</td>
<td>0.5 (0.2-1.1)</td>
<td>355 (99.3)</td>
<td>367 (90.2)</td>
<td>0.6 (0.3-1.0)</td>
<td>0.79</td>
<td></td>
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<tr>
<td>GSTT1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>+/-</td>
<td>83 (29.6)</td>
<td>75 (33.2)</td>
<td>1.0 (reference)</td>
<td></td>
<td>149 (39.1)</td>
<td>133 (31.2)</td>
<td>1.0 (reference)</td>
<td></td>
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<tr>
<td>++</td>
<td>147 (52.5)</td>
<td>107 (47.3)</td>
<td>0.8 (0.5-1.2)</td>
<td>176 (46.2)</td>
<td>217 (50.8)</td>
<td>1.4 (1.0-1.9)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>+/−</td>
<td>50 (17.9)</td>
<td>44 (19.5)</td>
<td>1.0 (0.6-1.7)</td>
<td>56 (14.7)</td>
<td>77 (18.0)</td>
<td>1.6 (1.0-2.4)</td>
<td>0.12</td>
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<tr>
<td>P&lt;sub&gt;trend&lt;/sub&gt; = 0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;sub&gt;trend&lt;/sub&gt; = 0.2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>+/- and --/-</td>
<td>197 (70.4)</td>
<td>151 (66.8)</td>
<td>0.9 (0.6-1.3)</td>
<td>232 (60.9)</td>
<td>294 (58.8)</td>
<td>1.4 (1.1-1.9)</td>
<td>0.05</td>
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</tr>
<tr>
<td>GSTP1—I105V</td>
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<tr>
<td>AA</td>
<td>132 (48.5)</td>
<td>97 (44.1)</td>
<td>1.0 (reference)</td>
<td></td>
<td>171 (44.1)</td>
<td>173 (40.8)</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>AG + GG</td>
<td>140 (51.5)</td>
<td>123 (55.9)</td>
<td>1.2 (0.9-1.8)</td>
<td>251 (56.9)</td>
<td>251 (59.2)</td>
<td>1.2 (0.9-1.6)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>GSTP1—A114V</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>238 (84.4)</td>
<td>189 (81.1)</td>
<td>1.0 (reference)</td>
<td></td>
<td>324 (83.3)</td>
<td>375 (87.2)</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>CT + TT</td>
<td>44 (15.6)</td>
<td>44 (18.9)</td>
<td>1.2 (0.8-2.0)</td>
<td>65 (16.7)</td>
<td>55 (12.8)</td>
<td>0.7 (0.5-1.1)</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, race, and gender.
and dietary sources of PAHs or hydrogenated amorphous carbons. Our analysis of dietary isothiocyanates from broccoli was difficult to interpret, possibly due to small numbers per subgroup and misclassification with respect to dietary exposure.

In conclusion, a lower risk of colorectal adenoma was observed among individuals carrying ≥1 inactive GSTM1 allele. Having ≥1 inactive GSTT1 allele was associated with a moderate increased risk among smokers. A significant interaction between ever smoking and genotype was observed when +/+ and −/− individuals were combined. GSTP1 variants were unrelated to risk. In summary, this is the first study to report associations between colorectal adenomas and GSTM1 wild-type and GSTT1 null alleles among smokers. These findings only became apparent using a newly developed assay to distinguish heterozygous and wild-type individuals. Our data provide evidence that phenotypic differences between these two groups exist.

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References
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