Homozygous Rapid Arylamine N-Acetyltransferase (NAT2) Genotype as a Susceptibility Factor for Lung Cancer

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ABSTRACT

The polymorphic arylamine N-acetyltransferase (NAT2) is supposed to be a susceptibility factor for certain malignancies. A phenotyping study in 389 lung cancer patients revealed a similar distribution of rapid and slow acetylators by the caffeine test to that in 657 reference subjects (odds ratio, 1.05; 95% confidence limits, 0.81, 1.36; not significant). A separate group of 155 lung cancer patients was studied by genotyping NAT2 and was compared with a matched reference group of 310 unrelated patients and 389 lung cancer patients. The NAT2 genotype was characterized by PCR-RFLP at nucleotide positions 191, 282, 341, 481, 590, 803, and 857. For evaluation of nucleotide 341, a 3'-mismatch primer was used. Homozygous wild-type genotypes NAT2*4*/4*4 were confirmed by DNA sequencing. Genotypes for rapid acetylation amounted to 43.9% among lung cancer and 41.6% among reference patients (odds ratio, 1.10; 95% confidence limits, 0.73, 1.65; not significant). Discrimination into homozygous and heterozygous carriers of allele NAT2*4 revealed a distinct overrepresentation of NAT2*4*/4*4 genotypes among lung cancer patients (odds ratio, 2.36; 95% confidence limits, 1.05, 5.32; P = 0.018). Logistic regression analysis considering sex, age, and smoking provided an odds ratio of 3.04 (95% confidence limits, 1.37, 6.75; P = 0.003). Hence, carriers of the NAT2*4*/4*4 genotype, with its especially high acetylation capacity, are at significantly increased risk to lung cancer.

INTRODUCTION

Hereditary susceptibility factors of bronchogenic carcinoma are being explored by molecular epidemiology studies to estimate the extent of an individual's risk. Several genetically polymorphic xenobiotic-metabolizing enzymes have been recently investigated. Certain genotypes, such as the 462IleVal mutation of CYP1A2 (1, 2) or deficiency of GSTM1 (3), were identified as a risk factor, whereas homozygous carriers of defective CYP2D6 (4, 5) may be partly protected from lung cancer. However, the role of these polymorphic enzymes in various malignancies is still being debated (6–8).

The low-activity variant of the polymorphic NAT2 is a recognized susceptibility factor for bladder cancer, especially for patients who were cigarette smokers or had been working in typical high-risk occupations (9, 10). Phenotyping studies correlating acetylation types and lung cancer failed to show an overrepresentation of slow acetylators. Instead, there is a slight trend of rapid acetylators being overrepresented (5, 11). Interestingly, such a trend also appeared in larynx cancer (12). In the light of the genotyping now available, rapid acetylators comprise homozygous and heterozygous carriers of the wild-type allele NAT2*4*4. Homozygotes have significantly higher acetylation rates than the heterozygotes (13). Moreover, studies with expression systems revealed highly varying Km and Vmax values for the five alleles coding slow acetylation (14, 15). Thus, the impact of distinct genotypes should be analyzed, irrespective of rapid or slow acetylation rates. This approach revealed that only NAT2*5B (not the other alleles coding for slow acetylation) is augmented in bladder cancer (9, 10). The implication of NAT2 in carcinogen metabolism might be different in bladder and lung cancer. The complex cooperation of NAT2 and NAT1 with CYP1A2 in forming highly reactive arylntrene ions from arylamine carcinogens (e.g., those contained in cigarette smoke) has been elucidated (16–18).

Here, we hypothesize that the slightly increased number of phenotypically rapid acetylators in lung cancer may be based on a significant increase of the relatively small subgroup of genotypically homozygous rapid acetylators. We reanalyzed and supplemented a previous phenotyping study and performed a genotyping case-control study in lung cancer patients and two control groups.

MATERIALS AND METHODS

Subjects of Investigation. The phenotyping study comprises 389 patients with lung cancer, namely 220 previously investigated patients (5) supplemented by 169 patients of the same catchment area. Reference patients (n = 657) had a variety of nonmalignant diseases and were recruited from the same hospitals (Lungenklinik Heckeshorn and Universitätsklinikum Steglitz, Berlin, Germany; see Table 1). To avoid any bias by ethnicity, all subjects were of German extraction, as judged by their names and place of birth. Histology of bronchogenic carcinomas followed the WHO classification and revealed 132 cases of squamous cell carcinoma, 77 of small cell carcinoma, 90 of large cell carcinoma, 66 of adenocarcinoma, and 24 of mixed cell carcinoma.

An additional group of 155 lung cancer patients entered a genotyping study (Lungenklinik Heckeshorn). They were matched by age (± 5 years, >5 years in 3 cases) and sex to 310 reference patients from the departments of Internal Medicine (Klinikum Steglitz and Klinikum Rudolf Virchow), Pneumology (Lungenklinik Heckeshorn), and Urology (Krankenhaus Neukölln) in Berlin. Most reference patients were hospitalized because of nonmalignant lung diseases, such as chronic obstructions, because of cardiovascular diseases, or with various urological diagnoses. A second control group was recruited from 278 healthy volunteers (see Table 1). Genotyped subjects were selected between 1991 and 1994. They gave their informed consent, and the study was approved by the Ethics Committee of the Klinikum Steglitz, Free University of Berlin. Both control groups were drawn from the anonymous DNA pool established in the Institute of Clinical Pharmacology (13). Total cigarette consumption is expressed in PYs (1 PY = consumption of 1 pack of 20 cigarettes per day for 1 year).

Determination of NAT2 Phenotype. The caffeine test (19) was applied as described (5). Briefly, patients ingested a cup of coffee, and acidified urine was collected for five h. Secondary caffeine metabolites, namely AFMU and 1X, were determined by reversed-phase high-performance liquid chromatography. Acetylation capacity was expressed as the molar ratio of AFMU and 1X. Rapid and slow acetylators were discriminated by an antimode of 0.5 (5, 13).

Identification of NAT2 Mutations and Alleles. Leukocytes from 10-mI venous blood samples were isolated, and DNA was extracted by a standard procedure (20). DNA fragments (1211 bp) containing the whole NAT2 gene were amplified by PCR. All mutations within the coding region were identified by PCR-RFLP analyses (13) with some modifications, outlined in Fig. 1. The
The mutations were detected by loss of the specified restriction site. Second, 0.1 μl of the CAAATGC (P100) and 5'-GTflTCTAGCATGAATCACTCTGC (P56). The fragment coding region (870 bp) was amplified with primers 5'-GTCACACGAGGAAAT CAAATCAGGAGAG (P87) and 5'-ACACAAGGGmAllTfGTTCC (P90), which covered a 32-bp fragment, coded by the mismatch-primer. Third, for evaluation of 5'90—sA evaluated by MspI and 282C—sT by FokI. 341T—sC was detected by the DdeI-cleavage cated; primer position is 342—373 nt). In the resulting 442-bp fragment. 191G—A was digested with TaqI or DdeI, respectively. The second and third PCR amplification product was also provided constitutive recognition motifs for MspI, DdeI, and TaqI, allowing an internal control for complete digestion.

Fig. 1. Genotyping procedure of NAT2. First, a 1211-bp fragment containing the whole coding region (870 bp) was amplified with primers 5'-GTCAACAGGAAAT CAAATGC (P100) and 5'-GTATTCTAAGAATCCTCTGC (P56). The fragment was digested with KpnI for evaluation of 481C—T and with BamHI for testing 857G—A. The mutations were detected by loss of the specified restriction site. Second, 0.1 μl of the PCR product was amplified by P100 and an antisense mismatch-primer 5'-ACCCAG CATAACATGATAATTGCCTCA (the mismatch base, C instead of G, is indicated; primer position is 342—373 nt). In the resulting 442-bp fragment, 191G—A was evaluated by MspI and 282C—T by FokI. 341T—C was detected by the DdeI-cleavage of a 32-bp fragment, coded by the mismatch-primer. Third, for evaluation of 590G—A and 803A—G, a 421-bp fragment was amplified, using nested primers 5'-CTTGGAC CAAATCGGAGG (P87) and 5'-ACACAAGGGmAllTfGTTCC (P90), which was digested with TaqI or DdeI, respectively. The second and third PCR amplification product also provided constitutive recognition motifs for MspI, DdeI, and TaqI, allowing an internal control for complete digestion.

mutational patterns were assigned to specified alleles (13, 21—24). The nomenclature follows Vatsis et al. (25). In cases in which the mutation pattern could theoretically indicate different allelic constellations, such as NAT2*4/*6A and NAT2*6B/*13, mutation linkage analyses were performed (13, 26). The mutation patterns were assigned to specified alleles (13, 21—24). The nomenclature follows Vatsis et al. (25). In cases in which the mutation pattern could theoretically indicate different allelic constellations, such as NAT2*4/*6A and NAT2*6B/*13, mutation linkage analyses were performed (13, 26).

DNA Sequencing. All samples with homozygous wild-type genotype were sequenced for the whole NAT2 coding region (13). Three overlapping fragments of the 1211-bp fragments were amplified by nested PCR. Double-strand DNA was processed using a Taq DyeDeoxy terminator sequencing kit (Applied Biosystems, Weiterstadt, Germany) and was analyzed with an Applied Biosystems 373A automated sequencer on a denaturing 6% polyacrylamide gel. Results were compared with the wild-type (NAT2*4/*4) sequence (27).

Statistics. Expected gene frequencies were calculated by the Hardy-Weinberg law from the allele frequencies in the control groups only. Statistical significance of differences between subgroups of cases and controls was calculated by the exact Fisher test (level of significance was P = 0.05). Odds ratios are given with 95% confidence limits and level of significance. Logistic regression analyses were performed using the BMDP program 7D (28). Sample sizes and type II error were calculated.

RESULTS

Rapid Acetylators among Phenotyped Subjects. The frequency of rapid acetylators in 389 lung cancer patients (48.3%; 95% confidence limits, 43.3%, 53.4%) was slightly higher than in 657 reference patients (47.0%; 95% confidence limits, 43.2%, 50.9%). The crude odds ratio was 1.05 (95% confidence limits, 0.81, 1.36). Logistic regression analysis considering age, sex, and smoking revealed an odds ratio for rapid acetylators of 1.17 (95% confidence limits, 0.86, 1.59; NS).

NAT2 in Genotyped Subjects. Point mutations at positions 341, 481, and 803 nt tended to be less frequent in lung cancer than in reference patients or healthy volunteers (Table 2). Combinations of these mutations constitute NAT2 alleles *5A, *5B, and *5C (Table 3). However, differentiation into heterozygous and homozygous rapid acetylation genotypes revealed a distinct overrepresentation of the NAT2*4 allele appeared more frequently in lung cancer patients than in either control group, with marginal significance (P = 0.094). Lung cancer patients provided 43.9% rapid acetylation genotypes, whereas 41.6% of the reference patients were carriers of this trait (odds ratio, 1.10; 95% confidence limits, 0.73, 1.65; NS; Table 4). However, differentiation into heterozygous and homozygous rapid acetylation genotypes revealed a distinct overrepresentation of the homozygous NAT2*4/*4 gene (11.0%) versus 4.8% in the reference group (crude odds ratio, 2.36; 95% confidence limits, 1.05, 5.32; P = 0.018). Heterozygous genotypes did not differ significantly (odds

Table 1. Lung cancer and reference patients included in the genotyping study and lung cancer patients, matched reference patients, and healthy volunteers included in the genotyping study.

<table>
<thead>
<tr>
<th>Phenotyping study</th>
<th>Genotyping study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Number</td>
<td>389</td>
</tr>
<tr>
<td>Male/female</td>
<td>313/76</td>
</tr>
<tr>
<td>Median age (range), yrs.</td>
<td>66 (33—84)</td>
</tr>
<tr>
<td>Male</td>
<td>65 (33—84)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (35—82)</td>
</tr>
</tbody>
</table>

Smoking

| Non-smokers       | 22              | 295         | 6            | 98         | 57                |
| 1—20 PY          | 63              | 165         | 29           | 86         | 29                |
| >20—50 PY        | 183             | 148         | 76           | 85         | 11                |
| >50 PY           | 119             | 49          | 44           | 41         | 0                 |
| Not available    | 2               | 0           | 0            | 0          | 182               |

Fig. 1. Genotyping procedure of NAT2. First, a 1211-bp fragment containing the whole coding region (870 bp) was amplified with primers 5'-GTCAACAGGAAAT CAAATGC (P100) and 5'-GTATTCTAAGAATCCTCTGC (P56). The fragment was digested with KpnI for evaluation of 481C—T and with BamHI for testing 857G—A. The mutations were detected by loss of the specified restriction site. Second, 0.1 μl of the PCR product was amplified by P100 and an antisense mismatch-primer 5'-ACCCAG CATAACATGATAATTGCCTCA (the mismatch base, C instead of G, is indicated; primer position is 342—373 nt). In the resulting 442-bp fragment, 191G—A was evaluated by MspI and 282C—T by FokI. 341T—C was detected by the DdeI-cleavage of a 32-bp fragment, coded by the mismatch-primer. Third, for evaluation of 590G—A and 803A—G, a 421-bp fragment was amplified, using nested primers 5'-CTTGGAC CAAATCGGAGG (P87) and 5'-ACACAAGGGmAllTfGTTCC (P90), which was digested with TaqI or DdeI, respectively. The second and third PCR amplification product also provided constitutive recognition motifs for MspI, DdeI, and TaqI, allowing an internal control for complete digestion.

Table 2. Frequency of NAT2 point mutations among 155 lung cancer patients as compared to 310 matched reference patients and 278 healthy volunteers.

<table>
<thead>
<tr>
<th>Position (nt)</th>
<th>Lung cancer (310 alleles)</th>
<th>Reference patients (620 alleles)</th>
<th>Healthy volunteers (556 alleles)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td>Frequency (%) Odds ratio *</td>
<td>Frequency (%) Odds ratio</td>
</tr>
<tr>
<td>191</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>282</td>
<td>31.6</td>
<td>31.5</td>
<td>1.01</td>
</tr>
<tr>
<td>341</td>
<td>41.0</td>
<td>45.3</td>
<td>0.84</td>
</tr>
<tr>
<td>481</td>
<td>38.1</td>
<td>41.9</td>
<td>0.85</td>
</tr>
<tr>
<td>590</td>
<td>29.7</td>
<td>28.4</td>
<td>1.02</td>
</tr>
<tr>
<td>803</td>
<td>37.1</td>
<td>40.8</td>
<td>0.81</td>
</tr>
<tr>
<td>857</td>
<td>1.94</td>
<td>2.10</td>
<td>0.92</td>
</tr>
</tbody>
</table>

* Odds ratios were calculated from the ratio of the number of alleles that are mutated at the position of interest versus the number of alleles not mutated at that position in lung cancer patients compared to the ratio in either control.
Table 3 NAT2 allele frequencies in 155 lung cancer patients compared with 310 matched reference patients and 278 healthy volunteers

<table>
<thead>
<tr>
<th>NAT2 allele</th>
<th>Lung cancer</th>
<th>Reference patients</th>
<th>Healthy volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>*4 (wt)</td>
<td>None</td>
<td>85</td>
<td>27.4</td>
</tr>
<tr>
<td>*5A</td>
<td>34, 481</td>
<td>12</td>
<td>3.9</td>
</tr>
<tr>
<td>*5B</td>
<td>34, 481, 803</td>
<td>106</td>
<td>34.2</td>
</tr>
<tr>
<td>*5C</td>
<td>34, 803</td>
<td>9</td>
<td>2.9</td>
</tr>
<tr>
<td>*6A</td>
<td>282, 590</td>
<td>6</td>
<td>1.9</td>
</tr>
<tr>
<td>*14B</td>
<td>191, 282</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>310</td>
<td>100.0</td>
<td>620</td>
</tr>
</tbody>
</table>

Odds ratios were calculated from the ratio of the number of alleles of interest versus all other alleles in lung cancer patients compared to the ratio in either control group. 

Stratification by Tumor Histology. There was no statistically significant overrepresentation of rapid acetylators among any histological subgroup within the phenotyped subjects (data not shown). In the genotypic study (Fig. 2), homozygous rapid acetylators were augmented in all subgroups, but statistically significantly only after further stratification by sex, namely in male patients with large-cell carcinoma (odds ratio, 4.24; 95% confidence limits, 0.84, 17.2; P = 0.04) and mixed-cell tumors (odds ratio, 5.19; 1.00, 22.0; P = 0.025). Fig. 2 also shows that heterozygous rapid acetylator genotypes only slightly varied in the subgroups.

DNA Sequencing and Verification of Mutation Linkage. All cancer cases genotyped as NAT2*4*/4 were confirmed by DNA sequencing. No new mutations were detected. Genes with NAT2*4*/4 of both control groups had been sequenced before (13). Mutation linkage analysis of the 22 cancer cases with NAT2*4*/4 always confirmed this genotype.

DISCUSSION

This study characterizes the homozygous rapid acetylator NAT2-genotype as a factor of increased susceptibility for lung cancer. To
ensure highest standard in correctness, all samples with this genotype were controlled by DNA sequencing. A hypothetical alternative mutation linkage in cases with NAT2*4/*6A was experimentally excluded. Moreover, nested-PCR methods were replaced by the more reliable PCR-RFLP technique (13). The sometimes critical detection of 341T→C is now based on the use of a mismatch primer leading to a restriction site in dependence of the mutation (Fig. 1). A second control group of healthy volunteers clearly conformed with the distribution of NAT2 genotypes observed in the matched reference patients, demonstrating that the reference group had a normal distribution that was close to proportions in other Caucasian groups (24, 29).

Three phenotyping studies had already shown that in lung cancer, the slow-acetylation trait is not overrepresented as it is the case in bladder cancer (9, 10). Odds ratios (rapid:slow) were 1.23 (126 cases; Ref. 11), 0.91 (53 cases; Ref. 30), and 1.12 (220 cases; Ref. 5). Our results in 389 cases are in line with these numbers. The observed trend of a slight overrepresentation of rapid acetylators also appears in our genotyping study (Table 4). Another genotyping study of 108 cases (31) is difficult to consider, as alleles with partly unconfirmed new mutation linkages are reported. Wild-type alleles, however, tended to be less frequent among cases. In contrast, preliminary genotyping data of 179 patients with laryngeal cancer (32) revealed an increased frequency of NAT2 alleles coding for rapid acetylation (odds ratio, 1.30; P = 0.093); the odds ratio for homozygous NAT2*4/*4 was 1.95 (P = 0.072). Additionally, in a separate study of 70 cases, the rapid phenotype predominated (odds ratio, 1.17; NS; Ref. 12). Laryngeal and lung cancer have most risk factors in common.

The differences in frequency of specific alleles (Table 3) or genotypes (Table 4) between cases and controls were statistically significant only for NAT2*4/*4. There is a trend of diminution of NAT2 alleles *5B and *5C (Table 3), which is again contrasting the constellation in bladder cancer (9, 10). Possibly, these alleles provide an enhanced affinity to arylamines involved in bladder cancer carcinogenesis (14, 15).

Strengthened by the above-mentioned literature, the experimental data suggests that NAT2 is decisively involved in the initiation of lung cancer, when present with very high activity as occurs in NAT2*4/*4 or *4/*2A. The rare allele NAT2*12A also codes for rapid acetylation.
Homozygous rapid acetylators provide significantly higher acetylation rates (mean AFMU/IX-ratio, 1.87; 95% confidence limits, 0.80, 4.39) than heterozygotes (AFMU/IX-ratio 1.23; 95% confidence limits, 0.34, 4.51; \( P < 0.001 \)) as shown in 563 Caucasian individuals (13). Heterozygotes (*4/4slow) were not found to be increased in lung cancer (Fig. 2). Only exceptionally high NAT2-activity may lead to an enhanced metabolic activation of precarcinogens. Further studies should clarify whether the high enzymatic capacity or high-affinity binding due to low \( K_m \) is crucial for the increased risk.

Subgroups of Lung Cancer Patients. Homozygous carriers of wild-type NAT2 were overrepresented among all histological subgroups (Fig. 2). It is interesting to note that the 17 cases of NAT2*4/*4 had relatively high age, were predominantly male, and had high cigarette consumption. Consideration of these three factors resulted in the highly significant multivariate odds ratio of 3.04 (\( P = 0.003 \)). It may be assumed that the combination of severe smoking and genotype NAT2*4/*4 constitutes a prime risk factor.

Impact of NAT2 in Arylamine Metabolism. Both phenotypes of acetylation capacity, rapid and slow, were shown as susceptibility factors for different carcinomas, due to distinct biochemical pathways of activation of carcinogens in the liver and locally in affected organs. Among bladder cancer patients, the slow acetylator trait was overrepresented, especially in cases with occupational exposure (9, 10, 12, 34, 35). This may be explained by the predominance of the competing hepatic \( N \)-oxidation in subjects with slow acetylation. Renally excreted aryl hydroxylamines are \( O \)-acetylated by local NAT1 so that arylhydroxynitrates ions, resulting in DNA adducts, can be formed (16, 36). On the other hand, slow acetylators might be less susceptible to colon cancer: after hepatic \( N \)-oxidation, aryl hydroxylamines may be \( O \)-acetylated by NAT1 and NAT2 (37), which are both expressed in colon mucosa (38, 39). Recently it was shown that a high-activity NAT1 allele is involved in bladder and colon carcinogenesis (40).

Human lung cancer may derive similarly via CYP1A2-catalyzed \( N \)-oxidation of arylamines in the liver and NAT-mediated \( N \)- and \( O \)-acetylation in lung tissue. The initial activation step via CYP1A2 may be enhanced by enzyme induction due to polycyclic hydrocarbons inhaled from cigarette smoke (41).

Increased risk of lung cancer for rapid acetylators by the outlined mechanism had been postulated by Lang and Kadlubar (16) and could now be confirmed in this study for the genetic group endowed with highest acetylation capacity. Because of the paucity of that trait in Caucasians, little is contributed to the estimation of a whole population’s risk; however, in a male individual with extensive smoking anamnesis, the diagnosis of NAT2*4/*4 should be cause for concern. It may be speculated that in other ethnic groups, such as Japanese, in which up to 40% are homozygous rapid acetylators (42), this genotype may be of general relevance for lung cancer risk.

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