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Polymorphisms in the *N*-acetyltransferase 1 (*NAT1*) gene and lung cancer risk in a minority population

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One of the most consistently observed exposure–disease relationship is the one between cigarette smoking and lung cancer. Aromatic amines and their metabolites are found in tobacco smoke and may be a class of carcinogen involved in lung carcinogenesis. The human *N*-acetyltransferase 1 (*NAT1*) enzyme can activate or deactivate aromatic amines, making it a candidate genetic susceptibility gene. We evaluated the potential role of the *NAT1* gene in lung cancer risk in a hospital-based case-control study in a minority population composed of Mexican- and African-Americans. We also assessed the potential interaction between *NAT1* and other environmental exposures such as cigarette smoking. There was no overall association between the *NAT1*10* genotypes and lung cancer risk. The adjusted odds ratio for the rapid acetylation genotypes was 0·72 (95 % CI 0·37–1·39) for *NAT1* defined as the presence of at least one copy of the *NAT1*10* allele when compared with all genotypes without the *NAT1*10* allele. Analyses by histological subtype or smoking history did not alter these findings. Other *NAT1* alleles will need to be studied for more conclusive results regarding the relevance of *NAT1* activity to lung carcinogenesis.

Keywords: *NAT1*, lung cancer, molecular epidemiology, ethnicity.

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Introduction

One of the most consistently observed exposure–disease relationships is that found between cigarette smoking and lung cancer. However, only a fraction of smokers develop lung cancer, which suggests that genetically determined factors may play a role in its aetiology. It has been observed that levels of biotransformation enzymes vary substantially between individuals due to both genetic and environmental influences. These differing rates of metabolism have been postulated to be important in modifying the risk of developing environmentally-induced diseases. As a result, numerous xenobiotic transformation enzymes have been targeted for study in relation to lung cancer.

One enzyme system of interest has been the *N*-acetyltransferases (NATs), which acetylate aromatic amines found in cigarette smoke such as 4-aminobiphenyl

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(4-ABP) (Patrianakos and Hoffman 1979). In humans, this acetylation activity is encoded by two independently regulated genes, *NAT1* and *NAT2* (Vatsis *et al.* 1995). Both gene loci are known to be polymorphic, and their catalytic activities include the N-acetylation of the aromatic amines (detoxification), as well as in the acetylation of N-hydroxylated metabolites to unstable acetoxy intermediates (activation) that can bind to DNA (Doll *et al.* 1997).

Phenotyping studies correlating acetylation phenotypes and lung cancer have not shown any conclusive relationship (Burgess and Trafford 1985, Philip *et al.* 1988, Roots *et al.* 1988, Ladero *et al.* 1991), although two studies have reported a modest association with rapid acetylators (Philip *et al.* 1988, Roots *et al.* 1988). More recently, an increased risk of lung cancer in subjects identified by genotyping as homozygous for the *NAT2*4* alleles (rapid acetylators) was observed in a case-control study conducted among Caucasians (Carcorbi *et al.* 1996). However, data on this association have also been inconsistent (Martinez *et al.* 1995, Oyama *et al.* 1997). One study, conducted in a Japanese population, reported an association between slow acetylation and lung cancer rather than with rapid acetylation. Similarly, an over-representation of mutations leading to slow acetylation phenotype has been reported among Spanish lung cancer cases (Martinez *et al.* 1995). However, the authors conclude that acetylator status does not appear to be a major factor in lung cancer risk.

The *NAT1* enzyme has also recently been shown to be polymorphically distributed in humans; the *NAT1* enzyme rather than *NAT2* was found to be expressed in the lung (Weber and Vatsis 1993, Grant *et al.* 1994,). Sequencing of variant *NAT1* alleles has identified a polymorphism at the polyadenylation signal of the *NAT1* gene (Vatsis and Weber 1993), which has subsequently been correlated with higher phenotypic expression (Bell *et al.* 1995a). Homozygous *NAT1*4* individuals were associated with 'normal' *NAT1* acetylation activity, whereas heterozygous and homozygous *NAT1*10* individuals had higher acetylation activity. Thus far, studies of this polymorphism have mostly been limited to cancers of the colorectum and bladder. Two studies have observed an increase in these cancers among subjects with the *NAT1**10 allele (Badawi *et al.* 1995, Bell *et al.* 1995b), but the data on these associations are sparse and conflicting (Okkels *et al.* 1997). One preliminary study by Chen *et al.* found a non-significant inverse association of the *NAT1*10* allele with lung cancer (Chen *et al.* 1996).

We investigated the hypothesis that the *NAT1* enzyme confers differential susceptibility to lung cancer, and assessed the potential modification of the association of cigarette smoking with lung cancer by acetylation status in a case-control study composed of a minority population.

Materials and methods

Study population

The cases and controls included in this report are from a hospital-based case-control study of lung cancer in minority populations described previously (Dave *et al.* 1995, Wu *et al.* 1995, Wiencke *et al.* 1997). The cases were newly diagnosed patients with histologically confirmed lung cancer who had not undergone radiotherapy or chemotherapy. Those who were enrolled also self-reported to be of African-American or Mexican-American ancestry. The patients were identified from The University of Texas M.D. Anderson Cancer Center and from county, community, and Veterans Administration hospitals in the Houston and San Antonio metropolitan areas. Controls were identified from a convenience sample recruited from community centres, cancer-screening programmes, churches, and employee groups. Only individuals without a history of cancer were eligible for participation as controls. The controls were

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frequency matched to the cases by gender, ethnicity, and age (5 years). A total of 493 blood samples were genotyped for the *NAT1* gene. The following results are based on 174 cases and 319 controls.

Data collection

After informed consent was obtained, interviews were conducted by trained interviewers/phlebotomists in English or Spanish. Data on sociodemographic characteristics, recent and past tobacco use, other lifestyle habits, occupational exposures and family history of cancer were collected. Ten ml of blood was drawn into heparinized tubes for molecular genetic analyses.

NAT1 genotyping

DNA was obtained from heparinized whole blood specimens after Qiagen extraction of DNA using the manufacturer's protocol. The samples were assayed without knowledge of case status. A modified method originally described by Bell *et al.* (Bell *et al.* 1995b) was used to identify *NAT1* polymorphic alleles. The buffer conditions used were as follows: 20 mM Tris–HCl, pH 8·6, 50 mM KCl, 2 mM MgCl2, and 0·1 % BSA. The samples were amplified under the following conditions: 35 cycles of 94°C for 30 s, 42°C for 30 s, 72°C for 45 s, with a final extension step of 5 min at 72°C. Currently, there are four relatively common polymorphic alleles for *NAT1*, designated *NAT1*3*, *NAT1**4, *NAT1**10, and *NAT1*11*. *NAT1*4* is the most common allele. *NAT1*10* is the putative 'rapid' allele (Bell *et al.* 1995a).

Statistical analysis

Logistic regression analysis was performed to assess the association between each of the *NAT1* genotypes and lung cancer. This analysis adjusted for the matching variables age, gender, and ethnicity and for pack-years smoked. For purposes of modelling the association between the *NAT1* gene and lung cancer, subjects who were homozygous or heterozygous for the *NAT1*10* allele were compared with those who did not have the *NAT1*10* allele. In addition, due to the hypothesis that individuals who are homozygous wild-type for the *NAT1*4* allele have 'normal' activity (Bell *et al.* 1995b), we created indicator variables for subjects who were heterozygous for the *NAT1*10* allele, homozygous for the *NAT1*10* allele, and who did not have the *NAT1*10* allele and compared these categories with the *NAT1*4/*4* genotype as the reference group.

The presence of effect modification by smoking was evaluated by use of stratified analysis. Due to the small number of non-smoking cases, all non-smokers were excluded from the analysis. Among smokers, light and heavy smokers were categorized by the 75th percentile pack-year value among controls (i.e. 30 pack-years and > 30 pack-years). We, then, calculated the association between the variant genotypes and lung cancer risk (i.e. risk ratios) within pack-year stratum to determine whether any particular genotype behaved differently at different levels of smoking exposure. Subjects who were homozygous wild-type *NAT1*4/*4* genotype served as the reference group within each smoking stratum.

All tests of statistical significance were two-sided. All analyses were performed with the SAS software package (SAS Institute Inc., Cary, NC).

Results

Sociodemographics and smoking history

The results of this study are based on 174 lung cancer cases and 319 controls for whom *NAT1* genotype information was collected. The sociodemographic characteristics and tobacco use of these subjects have been described in greater detail elsewhere (Dave *et al.* 1995, Wu *et al.* 1995, Wiencke *et al.* 1997). Briefly, of the 174 cases, 115 were African-Americans and 59 were Mexican-Americans. The mean age for both cases and controls was 62 years. Educational levels did not significantly differ by case status. When stratified by ethnicity, the African-Americans were slightly younger than the Mexican-American group and reported a greater educational attainment. As expected, there were significant differences in smoking history between cases and controls, but these observations did not differ by ethnicity.

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Table 1. *NAT1* allele frequency of controls by ethnicities.

NAT1 allele	Caucasians[a]	Hispanics	African-Americans	Asians[b]
*NAT1*4*	0·738	0·572	0·500	
*NAT1*10*	0·247	0·394	0·453	0·500
*NAT1*11*	0·016	0·008	0·011	
*NAT1*3*	N/A	0·025	0·036	

[a] Okkels *et al.* (1997).
[b] Probst-Hensch *et al.* (1996).

Table 2. *NAT1* genotype frequencies among cases and controls by ethnicity.

	Hispanics		African-Americans	
NAT1 genotype	Cases (n = 59)	Controls (180)	Cases (115)	Controls (139)
*NAT1*4/*4*	27·1 %	32·8 %	29·6 %	23·7 %
*NAT1*4/*11*	5·1	1·1	–	1·4
*NAT1*11/*11*	–	–	–	–
*NAT1*4/*10*	50·9	43·9	44·4	48·9
*NAT1*10/*10*	11·9	16·7	13·9	18·7
*NAT1*10/*11*	1·7	0·6	–	–
*NAT1*3/*4*	1·7	3·9	9·6	2·2
*NAT*3/*11*	–	–	–	0·7
*NAT*3/*10*	1·7	1·1	2·6	4·3

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NAT1 genotype and allele frequencies

Allele and genotype frequencies are described in tables 1 and 2 by ethnicity and case-status. The wild-type genotype (*NAT1*4/*4*) and allele (*NAT1*4*) frequencies are similar between ethnicities, but are less common than those reported in Caucasians (Probst-Hensch *et al.* 1996, Okkels *et al.* 1997).

NAT1 genotypes and lung cancer

No overall association between the presumed 'at risk' *NAT1*10* allele and lung cancer was observed in this study population. The adjusted odds ratio was 0·72 (95 % CI 0·37–1·39) when comparing subjects who had at least one *NAT1*10* allele compared with subjects who did not carry the allele. Analyses by histological subtype did not alter these findings (data not shown). However, when comparisons were made in reference to subjects who were *NAT1*4/*4* (wild-type), the adjusted odds ratios for the individuals who were heterozygous for the *NAT1*10* allele, homozygous for the *NAT1*10* allele, and who did not have the *NAT1*10* allele were 1·34 (95 % CI 0·77–2·31), 0·95 (95 % CI 0·46–1·96), and 3·04 (95 % CI 1·04–8·90), respectively (table 3). Moreover, subjects who were homozygous for the *NAT1*10* allele were not at greater risk of developing lung cancer than individuals who were heterozygous for the *NAT1*10* allele. In addition, among Mexican-Americans an increase in lung cancer risk was observed among individuals who were heterozygous for the *NAT1*10* allele when compared with subjects who were *NAT1*4/*4* wild-type (OR = 2·36, 95 % CI 0·99–5·63).

NAT1 genotypes, cigarette smoking exposure, and lung cancer

Interaction between cumulative cigarette smoking dose (as estimated by lifetime pack-years smoked) and *NAT1* on lung cancer risk was also assessed (table 4). No

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Table 3. Odds ratios and 95 % confidence intervals between *NAT1* and lung cancer risk.

NAT1 genotype	Cases	Controls	Adjusted OR (95 % CI)[a]
*NAT1*4/*4*	50	92	1·0 (ref)
*NAT1*10*/any[b]	86	156	1·34 (0·77–2·31)
*NAT1*10/*10*	23	56	0·95 (0·46–1·96)
All others[c]	15	15	3·04 (1·04–8·90)
Mexican-American			
*NAT1*4/*4*	16	59	1·0 (ref)
*NAT1*10*/any	32	82	2·36 (0·99–5·63)
*NAT1*10/*10*	7	30	1·56 (0·48–5·03)
All others	4	9	8·49 (1·34–53·8)
African-American			
*NAT1*4/*4*	34	33	1·0 (ref)
*NAT1*10*/any	54	74	0·94 (0·45–1·97)
*NAT1*10/*10*	16	26	0·71 (0·27–1·86)
All others	11	6	1·80 (0·48–6·71)
Squamous			
*NAT1*4/*4*	19	92	1·0 (ref)
*NAT1*10*/any	23	156	0·82 (0·34–1·98)
*NAT1*10/*10*	9	56	0·78 (0·25–2·42)
All others	3	15	0·77 (0·12–4·80)
Adenocarcinoma			
*NAT1*4/*4*	18	92	1·0 (ref)
*NAT1*10*/any	29	156	1·10 (0·53–2·31)
*NAT1*10/*10*	6	56	0·64 (0·22–1·87)
All others	3	15	1·03 (0·21–5·15)

[a] Unconditional logistic regression adjusted for the age, ethnicity, gender and pack-years smoked.
[b] All subjects who are heterozygous for the *NAT1*10* allele.
[c] All subjects who do not have the *NAT1*10* allele.

Table 4. Odds ratios and 95 % confidence intervals between *NAT1* and lung cancer risk stratified by pack-years smoked[a].

NAT1 genotype	Pack-years smoked	Cases	Controls	Adjusted[b] OR (95 % CI)
*NAT1*4/*4*	<30	12	42	1·0 (ref)
No *NAT1*10*[c]	<30	6	3	5·56 (1·16–26·6)
Het[d]	<30	26	59	1·41 (0·63–3·17)
Variants[e]	<30	10	26	1·34 (0·50–3·60)
*NAT1*4/*4*	<30	37	13	1·0 (ref)
No *NAT1*10*	<30	8	2	0·99 (0·18–5·59)
Het	<30	54	18	0·96 (0·41–2·24)
Variants	<30	13	7	0·55 (0·17–1·77)

[a] Restricted to smokers.
[b] Unconditional logistic regression adjusted for the matching variables age, gender, and ethnicity.
[c] Subjects who do not have the *NAT1*10* allele.
[d] 'Hets' are subjects who have one *NAT1*10* allele.
[e] 'Variants' are all subjects who are homozygous for the variant *NAT1*10* allele.

increase in lung cancer risk was observed for subjects who had one or more *NAT1*10* allele when compared with homozygous wild-type individuals at either smoking level. However, an increase in risk cannot be excluded for individuals who do not have the polyadenylation signal polymorphism at lower smoking exposure (30 pack-years; risk ratio = 5·56, 95 % CI 1·16–26·6).

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Discussion

In this study of 171 lung cancer cases and 319 controls, we did not observe an increase in lung cancer risk among subjects who were homozygous or heterozygous for the *NAT1*10* allele regardless of histology, supporting studies reported previously (Chen *et al.* 1996). However, an excess in lung cancer risk was observed among subjects who were *NAT1*3/*4*, *NAT1*4/*11*, or *NAT1*3/*11*, suggesting that another allele may give rise to differences in phenotypic expression. There are data to suggest that other alleles may be involved in differences in acetylation (Grant *et al.* 1994, Bell *et al.* 1995a, de Leon *et al.* 1996, Doll *et al.* 1997).

The allele frequencies of *NAT1* did not differ significantly between Mexican- and African-Americans, as has been previously reported for the *NAT1*10* (Probst-Hensch *et al.* 1996). However, the distributions of these alleles were considerably different from those previoulsy reported in Caucasians (Probst-Hensch *et al.* 1996). The presumed 'at risk' *NAT1*10* allele is much more common in Mexican- and African-Americans than in Caucasians (approximately 0·40 compared with 0·25). Even with this increase in prevalence (and subsequent increase in power), no increase in lung cancer risk for subjects who were heterozygous or homozygous for the *NAT1*10* allele was observed.

The lack of an association between *NAT1*10* polymorphism and lung cancer, if real, could mean that aromatic amines are not important lung carcinogens in humans. Although these results are consistent with data reported from biomarker studies where the adducts that have been observed in lung tumours have generally been PAHs in origin rather than aromatic amine, limitations in this study need to be addressed.

One possible reason for the lack of association observed is the recent identification of other alleles in the *NAT1*. It has previously been reported that the concordance between NAT1 phenotype and genotype is 70 % (Badawi *et al.* 1995). Allelic variants *NAT1*14* and **15* have also been reported to produce defective *NAT1* proteins and lead to functional impairment in the metabolism of *NAT1*-selective substrates both *in vivo* and *in vitro* (Grant *et al.* 1997). If these alleles play a role in determining phenotypic expression, the current method used would lead to misclassification of this exposure. It has been demonstrated that small differences in genetic marker misclassification can produce substantial bias (Rothman *et al.* 1993).

Another potential limitation is that the information presented here has not been analysed in combination with *NAT2* data. Due to some substrate overlaps, this may be a source of bias that has not been controlled. However, it is generally believed that *NAT1* is involved in the acetylation of simple aromatic amines, such as those found in cigarette smoke (Vatsis *et al.* 1994). At the same time, *NAT2* is not known to be expressed in the lung, and hence, the combination of *NAT1* and *NAT2* genotypes may not be biologically relevant. However, one cannot dismiss the possible role that hepatically expressed NAT2 may play in arylamine metabolism.

In summary, we did not observe an association between the putative 'at risk' *NAT1*10* allele and lung cancer risk in this minority population. Although a statistically significant association was observed for the *NAT1*3/*4, NAT1*4/*11*, and *NAT1*3/*11* genotypes; due to multiple comparisons that have been made, these results are most likely due to chance. However, further investigation on the functional properties of these and other *NAT1* allelic variants is necessary to determine the potential role of this enzyme in lung cancer risk.

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