N-Acetyl Transferase Genotypes in Relation to Risk of Developing Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To examine the association between N-acetyl transferase (NAT) genotype (NAT1 and NAT2) and risk of developing systemic lupus erythematosus (SLE).

Methods. DNA samples were collected from 243 recently diagnosed cases and 298 controls enrolled in a population based case-control study conducted in 60 counties in North Carolina and South Carolina, USA.

Results. There was no association between SLE and NAT1 genotype (OR 0.96, 95% CI 0.65, 1.4 for the presence of a *10 allele) or NAT2 genotype (OR 1.1, 95% CI 0.73, 1.6 for the slow- compared with fast-acetylation genotype). We saw some evidence of interaction between NAT genotypes and use of hair dyes (a source of arylamines), with higher risk seen among hair dye users who had both the *10 NAT1 allele and the NAT2 slow-acetylation genotype (OR 2.9, 95% CI 1.2, 6.9 in this subgroup compared with all others).

Conclusion. Our results suggest that although there is little overall association between NAT genotypes and risk of developing SLE, the interaction between NAT1 and NAT2 and specific exposures such as hair dyes may be important. This finding highlights the need to consider exposure when assessing genetic susceptibility. (J Rheumatol 2004;31:76–80)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS AUTOIMMUNE DISEASE
N-ACETYL TRANSFERASE METABOLISM TOBACCO ARYLAMINES

Metabolism of arylamines, e.g., from hair dye and smoking, is complex. Two N-acetyl transferase (NAT) isozymes, NAT1 and NAT2, catalyze both N-acetylation and O-acetylation of arylamines. NAT2 is most highly expressed in liver, and the N-acetylation pathway would lead to a less reactive moiety. Several relatively common alleles of NAT2 when inherited together confer a "slow" acetylation phenotype activity (normal activity is classified as "fast")[1]. NAT1 expression is tissue-specific and more variable, but expression has been shown to occur in the bladder and in leukocytes[2,3]. NAT1 is also highly polymorphic. Inheritance of one or more copies of the NAT1*10 allele has been reported to be associated with increased NAT activity[1], although this has not been a consistent finding[4]. Slow acetylation by NAT2 and increased O-acetylation by NAT1 would be expected to lead to an increased presence in the blood of more highly reactive metabolites[5].

NAT activity has been associated with the development of drug-induced lupus, with slow acetylation conferring higher risk for developing specific autoantibodies or other features of this condition[6,7]. Two recent studies reported no association between NAT2 phenotype or genotype in relation to disease risk[8,9], but von Schmiedeberg, *et al* reported a higher prevalence of slow NAT2 phenotypes among 88 patients with SLE (and 26 with systemic sclerosis) compared with controls representing a healthy German population[10]. The possible effect of the disease, particularly if kidney involvement is present, on the phenotypic assessment of NAT activity (based on determination of urinary metabolites obtained after ingestion of a caffeine-containing drug or beverage) is a potential limitation of some of the previous studies.

The Carolina Lupus Study is a population based case-control study designed to assess the role of hormonal, environmental, and genetic risk factors for SLE[11,12]. Smoking was not associated with risk of SLE in this study, but there

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was a weak association between disease risk and use of permanent hair dyes (OR 1.5, 95% CI 1.0, 2.2 among women, and OR 1.4, 95% CI 1.0, 2.1 for the full sample of men and women)[12]. We used data from the Carolina Lupus Study to analyze the association between NAT1 and NAT2 genotypes and SLE, and to assess the interaction between NAT1 and NAT2 genotypes and use of permanent hair dyes. The specific hypotheses were that the presence of a *10 NAT1 allele and the slow-acetylation NAT2 genotype would be associated with risk of SLE, and that this risk would be highest in conjunction with use of permanent hair dyes.

MATERIALS AND METHODS

The Carolina Lupus Study was based in 60 contiguous counties in eastern and central North Carolina and South Carolina. Patients with recently-diagnosed SLE were identified through community based rheumatologists and university based rheumatology practices in the study area.

Population based controls were identified through driver's license records and were frequency-matched to the cases by age (5-year age groups), sex, and state. The study protocol was approved by the review boards of all participating institutions. Details of the recruitment procedures and demographic characteristics of participants have been described[11]. Ninety percent of the 265 SLE cases in the Carolina Lupus Study were female, 60% were African American, and the mean age at diagnosis was 39 years[13]. The frequency of clinical-immunologic and clinical features is similar to other lupus cohorts[14]. Data collection included a structured 60-minute in-person interview[12]. We obtained one blood sample from 244 (92%) cases and 303 (85%) controls.

DNA was obtained from previously frozen blood samples following standard methods, and DNA samples were available for 243 cases and 298 controls.

Samples were genotyped for the NAT1*3, NAT1*4, and the putative high-activity NAT1*10 allele, along with NAT2*4, NAT2*5, NAT2*6, NAT2*7, and NAT2*14 (the most common functional and low-activity alleles that are frequently referred to as WT, M1, M2, M3, and M4, respectively). Genotyping was accomplished by polymerase chain reaction (PCR) amplification of the relevant polymorphic sites followed by a second primer extension reaction that generates products of different lengths depending on the relevant single nucleotide polymorphisms (SNP) being investigated. The mass and abundance of these fragments were determined by matrix assisted laser desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry, which in turn provided the precise genotype. All samples were run blindly with appropriate known genotype control samples and negative controls.

We conducted separate analyses among African Americans and among whites because of racial difference in distribution of NAT genotype. The association between genotype and risk of developing SLE was estimated by the odds ratio and 95% confidence interval using logistic regression and adjusting for age, sex, and state. For analyses for which there was no statistically significant effect modification by race (interaction p value > 0.15), we also conducted analyses of the full sample, using a 2-level variable (whites, African Americans and other minorities) to adjust for ethnicity.

RESULTS

There was no association between sex or age and frequency of NAT1 or NAT2 genotype among controls, but the wild-type (no *10 allele) NAT1 genotype and the slow-acetylation NAT2 genotypes were more common among whites compared with African Americans. Allele frequencies of cases and of controls were both in Hardy-Weinberg equilibrium.

There was little evidence of an association between SLE and NAT1 or NAT2 genotype in the full sample or in analyses stratified by race (Table 1). Adjusting for NAT1 had little effect on the estimate of the NAT2 effect, and adjusting for NAT2 had little effect on the NAT1 association (data not shown).

We saw some evidence of interaction between NAT1*10 genotype and use of hair dyes (interaction p value = 0.031), with a higher risk seen among users of hair dyes who were carriers of a *10 allele (OR 1.4). Although the effect modification between NAT2 genotype and use of hair dyes was not statistically significant (interaction p value = 0.34), the strongest association was seen among NAT2 slow-acetylation genotypes (OR 1.4) (Table 2). In the 3-way interaction, the combination of presence of NAT1*10 allele in conjunction with slow NAT2 acetylation genotype and hair dye use was the group that showed evidence of an increased risk of SLE (OR 2.4) (Table 3). Comparing this group to all others resulted in a statistically significant association (OR 2.9,

Table 1. Associations between NAT1 and NAT2 genotype and risk of developing SLE*.

	Total Sample†, 243 Cases, 298 Controls			African Americans, 144 Cases, 73 Controls			Whites, 85 Cases, 202 Controls		
	Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Controls, n (%)	OR (95% CI)
NAT1*10									
*10 allele absent	102 (42)	158 (53)	1.0 (referent)	39 (27)	16 (22)	1.0 (referent)	56 (66)	132 (65)	1.0 (referent)
*10 allele present	141 (58)	138 (47)	0.96 (0.65, 1.4)	105 (73)	56 (78)	0.77 (0.39, 1.5)	29 (34)	70 (35)	0.98 (0.57, 1.7)
NAT2									
Fast	118 (51)	130 (46)	1.0 (referent)	82 (58)	44 (64)	1.0 (referent)	31 (41)	78 (40)	1.0 (referent)
Slow	112 (49)	151 (54)	1.1 (0.73, 1.6)	60 (42)	25 (36)	1.2 (0.68, 2.3)	45 (59)	115 (59)	1.0 (0.60, 1.8)

* Odds ratio and 95% confidence interval estimated by logistic regression adjusting for age, sex, and state. Analyses for the full sample also adjust for race as a 2-level variable (whites, African Americans and other minorities). † Total sample includes other minorities (14 cases, 23 controls) in addition to African Americans and whites. Missing data: NAT1, one African American and one other minority control; NAT2, 9 white cases, 9 white controls, 2 African American cases, 4 African American controls, 2 other minority cases, 4 other minority controls.

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Table 2. Association between risk of SLE in conjuction with hair dye use and NAT1 and NAT2 genotypes*.

Hair Dye Use	Genotype	Total Sample†, 243 Cases, 298 Controls			African Americans, 144 Cases, 73 Controls			Whites, 85 Cases, 202 Controls		
		Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Contols, n (%)	OR (95% CI)
No	NAT1*10 absent	68 (28)	93 (31)	1.0 (referent)	29 (20)	11 (15)	1.0 (referent)	34 (40)	79 (39)	1.0 (referent)
No	NAT1*10 present	99 (41)	108 (36)	0.74 (0.46, 1.2)	76 (53)	46 (64)	0.62 (0.38, 1.4)	18 (21)	51 (25)	0.85 (0.43, 1.7)
Yes	NAT1*10 absent	34 (14)	65 (22)	0.78 (0.45, 1.4)	10 (7)	5 (7)	0.68 (0.19, 2.5)	22 (26)	53 (26)	1.1 (0.57, 2.2)
Yes	NAT1*10 present	42 (17)	30 (10)	1.4 (0.75, 2.6)	29 (20)	10 (14)	1.1 (0.38, 3.0)	11 (13)	19 (9)	1.5 (0.65, 3.7)
No	NAT2 fast	86 (37)	93 (33)	1.0 (referent)	60 (43)	33 (48)	1.0 (referent)	22 (29)	55 (29)	1.0 (referent)
No	NAT2 slow	72 (31)	99 (35)	0.94 (0.60, 1.5)	44 (31)	21 (30)	1.1 (0.55, 2.1)	24 (32)	71 (37)	0.87 (0.43, 1.7)
Yes	NAT2 fast	32 (14)	37 (13)	1.0 (0.54, 1.8)	22 (15)	11 (16)	1.0 (0.43, 2.4)	9 (12)	23 (12)	1.1 (0.44, 2.9)
Yes	NAT2 slow	40 (17)	52 (19)	1.4 (0.79, 2.5)	16 (11)	4 (6)	2.1 (0.63, 6.9)	21 (28)	44 (23)	1.5 (0.70, 3.2)

* Odds ratio and 95% confidence interval estimated by logistic regression adjusting for age, sex, and state. † Total sample includes other minorities (14 cases, 23 controls) in addition to African Americans and whites, and the model also includes race as a 2-level variable (whites, African Americans and other minorities). Missing data: NAT1, one African American and one other minority control; NAT2, 9 white controls, 2 African American cases, 4 African American controls, 2 other minority cases, 4 other minority controls. The interaction between NAT genotype and hair dye use, evaluated by comparison of the –2 log-likelihood statistic in models with and without the interaction variable was p = 0.030 for NAT1 and p = 0.34 for NAT2.

Table 3. Interaction between hair dye use, NAT1 and NAT2 genotypes, and risk of developing SLE*.

Hair Dye Use	NAT2	NAT1 *10 Allele	Total Sample†, 230 Cases, 281 Controls			African Americans, 142 Cases, 69 Controls			Whites, 76 Cases, 193 Controls		
			Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Contols, n (%)	OR (95% CI)
No	Fast	Absent	28 (12)	36 (13)	1.0 (referent)	13 (9)	6 (9)	1.0 (referent)	12 (16)	30 (16)	1.0 (referent)
No	Fast	Present	58 (25)	57 (20)	0.73 (0.37, 1.4)	47 (33)	27 (39)	0.76 (0.26, 2.3)	10 (13)	25 (13)	1.0 (0.38, 2.9)
No	Slow	Absent	35 (15)	52 (19)	0.98 (0.48, 2.0)	16 (11)	4 (6)	1.6 (0.37, 7.2)	18 (24)	46 (24)	1.0 (0.42, 2.4)
No	Slow	Present	37 (16)	47 (17)	0.62 (0.30, 1.3)	28 (20)	17 (25)	0.69 (0.22, 2.2)	6 (8)	25 (13)	0.64 (0.20, 2.0)
Yes	Fast	Absent	10 (4)	17 (6)	0.77 (0.28, 2.1)	4 (3)	2 (3)	0.80 (0.11, 5.7)	5 (7)	13 (7)	1.1 (0.32, 4.0)
Yes	Fast	Present	22 (10)	20 (7)	0.83 (0.35, 2.0)	18 (13)	9 (13)	0.81 (0.22, 2.9)	4 (5)	10 (5)	1.1 (0.29, 4.5)
Yes	Slow	Absent	22 (10)	42 (15)	0.85 (0.39, 1.9)	6 (4)	3 (4)	0.77 (0.14, 4.3)	15 (20)	35 (18)	1.3 (0.52, 3.4)
Yes	Slow	Present	18 (8)	10 (4)	2.4 (0.88, 6.5)	10 (7)	1 (1)	4.5 (0.45, 45.4)	6 (8)	9 (5)	2.2 (0.62, 7.8)

* Odds ratio and 95% confidence interval estimated by logistic regression adjusting for age, sex, and atate. † Total sample includes other minorities (12 cases, 19 controls) in addition to African Americans and whites, and the model also includes race as a 2-level variable (whites, African Americans and other minorities).

95% CI 1.2, 6.9). Similar patterns were seen in separate analyses for African Americans and whites.

Among patients, there was no association between NAT2 genotype and prevalence of most of the clinical and immunologic features we examined (Table 4). Although anti-dsDNA antibodies and renal involvement are not commonly seen in drug-induced lupus, these features were somewhat more common in the NAT2 slow-acetylation group.

DISCUSSION

Although we observed little evidence of an association between SLE risk and NAT1 or NAT2 genotypes in the total study population, there was some indication of an interaction with use of hair dyes. Specifically, there was evidence for an association with hair dye use in conjunction with slow NAT2 activity and the *10 NAT1 allele (which may confer higher NAT1 activity). This is the genotype combination we had identified *a priori* as most susceptible to a potential exposure effect because this combination of slow acetylation in the liver and high acetylation in the leukocytes could lead to an increased presence of high reactive species. These results may represent a chance finding, since multiple groups were examined, so it is important to replicate this analysis in other studies.

Strengths of the study include its relatively large size, the inclusion of African Americans and whites (and the separate analyses performed in these groups), the use of PCR-derived NAT genotype data, which are unlikely to be affected by disease status or activity, and the analysis of potential inter-

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Table 4. NAT2 genotype and features of SLE among patients*.

	Total Sample†, N = 112 Slow, 118 Fast			African Americans, N = 60 Slow, 82 Fast			Whites, N = 45 Slow, 31 Fast		
	Slow, n (%)	Fast, n (%)	OR (95% CI)	Slow, n (%)	Fast, n (%)	OR (95% CI)	Slow, n (%)	Fast, n (%)	OR (95% CI)
Autoantibodies									
Anti-dsDNA	35 (31)	29 (25)	1.5 (0.80, 2.7)	24 (40)	23 (28)	1.7 (0.81, 3.4)	9 (20)	6 (19)	0.87 (0.27, 2.8)
Anti-Ro	52 (46)	36 (31)	2.1 (1.2, 3.7)	28 (47)	28 (34)	1.6 (0.81, 3.2)	18 (40)	7 (23)	2.4 (0.81, 6.9)
Anti-La	10 (9)	13 (11)	0.85 (0.34, 2.1)	4 (7)	9 (11)	0.60 (0.17, 2.1)	4 (9)	4 (13)	0.65 (0.14, 3.0)
Anti-RNP	24 (21)	42 (36)	0.57 (0.30, 1.1)	23 (38)	38 (46)	0.70 (0.35, 1.4)	0 (0)	3 (10)	—‡
Anti-Sm	16 (14)	15 (13)	1.4 (0.64, 3.1)	15 (25)	13 (16)	1.7 (0.74, 4.0)	1 (2)	1 (3)	1.1 (0.05, 21.9)
Clinical features									
Proteinuria	28 (26)	29 (25)	1.4 (0.73, 2.7)	21 (37)	22 (28)	1.6 (0.77, 3.5)	4 (9)	6 (19)	0.64 (0.15, 2.8)
Serositis	47 (44)	47 (41)	1.2 (0.70, 2.1)	24 (42)	36 (45)	0.91 (0.46, 1.8)	19 (43)	11 (37)	1.4 (0.52, 3.7)
Pleuritis	43 (40)	39 (34)	1.4 (0.79, 2.4)	23 (40)	28 (35)	1.3 (0.63, 2.6)	16 (36)	11 (37)	1.1 (0.41, 3.0)
Pericarditis**	19 (18)	14 (12)	1.9 (0.86, 4.1)	12 (21)	14 (18)	1.3 (0.54, 3.2)	5 (11)	0 (0)	—‡
Neuropsychiatric	9 (8)	4 (4)	2.8 (0.81, 9.6)	7 (12)	4 (5)	2.6 (0.70, 9.7)	2 (5)	0 (0)	—‡
Hemolytic anemia**	11 (10)	13 (11)	1.1 (0.43, 2.6)	7 (12)	11 (13)	0.87 (0.29, 2.6)	4 (9)	2 (6)	1.5 (0.23, 9.4)
Leukopenia**	20 (18)	22 (19)	1.2 (0.57, 2.3)	12 (20)	17 (21)	0.99 (0.42, 2.3)	6 (13)	5 (16)	1.3 (0.29, 5.5)
Lymphopenia**	23 (21)	29 (25)	0.95 (0.49, 1.8)	15 (25)	20 (24)	1.2 (0.50, 2.8)	6 (13)	9 (29)	0.40 (0.12, 1.3)
Thrombocytopenia	6 (6)	19 (16)	0.36 (0.13, 0.97)	3 (5)	12 (15)	0.33 (0.09, 1.2)	3 (7)	6 (19)	0.68 (0.12, 3.8)
Malar rash	43 (40)	44 (38)	1.0 (0.57, 1.7)	19 (33)	29 (36)	0.87 (0.42, 1.8)	22 (50)	13 (43)	1.3 (0.48, 3.3)
Discoid rash	20 (19)	15 (13)	2.1 (0.95, 4.5)	15 (26)	15 (19)	1.6 (0.70, 3.7)	3 (7)	0 (0)	—‡
Photosensitivity	40 (38)	46 (40)	0.83 (0.47, 1.5)	18 (32)	26 (33)	0.99 (0.47, 2.1)	21 (49)	17 (55)	0.84 (0.32, 2.2)
Oral ulcers	17 (16)	22 (19)	0.73 (0.35, 1.5)	8 (14)	11 (14)	0.97 (0.36, 2.6)	7 (16)	8 (26)	0.51 (0.16, 1.7)
Arthritis	74 (69)	93 (80)	***	37 (64)	66 (83)	0.36 (0.16, 0.82)	33 (75)	23 (74)	1.1 (0.38, 3.4)

* Logistic regression, adjusting for age and sex, estimating odds ratio and 95% confidence interval for the association between genotype and presence of specific autoantibody. † Analysis of total sample includes 12 other minorities (7 slow-acetylation and 5 fast-acetylation genotype) in addition to African Americans and whites, and the model also includes race as a 2-level variable (whites, African Americans and other minorities). ‡ OR not calculated because of zero cell. ** Analysis of pericarditis, hemolytic anemia, leukopenia, and lymphopenia also adjusted for physician type (university, community-based rheumatologist), as described[14]. *** Summary OR for full sample not calculated because of effect-modification by race (interaction p value = 0.14).

action with a relatively common source of arylamine exposures. The prevalence of slow-acylation NAT2 genotypes among white controls (59%) was similar to the prevalence reported in controls in a recent study from Germany[9], and the prevalence of the NAT1*10 allele was similar to data from another population based case-control study in North Carolina[15]. However, the sample size was not large enough to definitely assess the potential hair dye interaction. We obtained information about usual color of dye used, but we did not collect information on specific brands and products. Only 10% of cases and 5% of controls reported use of dark-color dyes[11], so it is not possible to further refine this exposure to focus more clearly on the arylamine content of this exposure.

The "high risk" group (hair dye users who had the NAT1*10 allele and the NAT1 slow-acetylation genotype) is relatively small (8% of cases, 4% of controls). This interaction, if replicated in other studies, may not be a major risk factor for SLE, but it underscores the need to consider gene-environment and multi-way interactions to fully elucidate the etiology of SLE.

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