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Effect of Glutathione S-Transferase Polymorphisms and Proximity to Hazardous Waste Sites on Time to Systemic Lupus Erythematosus Diagnosis

Results From the Roxbury Lupus Project

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Objective. **The high prevalence of systemic lupus erythematosus (SLE) among African American women may be due to environmental exposures, genetic factors, or a combination of factors. Our goal was to assess association of residential proximity to hazardous waste sites and genetic variation in 3 glutathione S-transferase (GST) genes (GSTM1, GSTT1, and GSTP1) with age at diagnosis of SLE.**

Methods. **Residential histories were obtained by interviewing 93 SLE patients from 3 predominantly African American neighborhoods in Boston. Residential addresses and locations of 416 hazardous waste sites in the study area were geocoded using ArcView software. Time-varying Cox models were used to study the effect of residential proximity to hazardous sites, GST genotype, and interaction between genotype and exposure in determining age at diagnosis.**

Results. **The prevalence of SLE among African American women in these neighborhoods was 3.56 SLE cases per 1,000. Homozygosity for GSTM1-null and GSTP1 Ile105Val in combination was associated with earlier SLE diagnosis ($P = 0.03$), but there was no association with proximity to 416 hazardous sites. Available data on specific site contaminants suggested that, at a subset of 67 sites, there was higher potential risk for exposure to volatile organic compounds ($P < 0.05$ with Bonferroni correction). GST genotypes had a significant interaction with proximity ($P = 0.03$) in analyses limited to these sites.**

Conclusion. **There was no independent association between residential proximity to hazardous waste sites and the risk of earlier SLE diagnosis in this urban population. However, analysis of a limited number of sites indicated that the risk of earlier SLE associated with proximity to hazardous sites might be modulated by GST polymorphisms.**

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Systemic lupus erythematosus (SLE) is an autoimmune systemic rheumatic disease that occurs predominantly in women, especially those of African descent (1–6). Twin studies have suggested that heritability accounts for 30–40% of the overall susceptibility to SLE (7); other "nongenetic" or environmental factors may also be involved in SLE etiology. A variety of susceptibility genes have been identified (8–13); however, none of the genes identified to date adequately explain the elevated risk of SLE observed in people of sub-Saharan African ancestry.

Potential environmental triggers of SLE include ultraviolet radiation, xenobiotic organic and inorganic compounds, silica dust, infectious agents, and endogenous and exogenous sex hormones (14–16). Exposure to organic solvents, petroleum, and related by-products may play a role in susceptibility to SLE (17–22). Solvent exposure has been associated with the risk of other autoimmune diseases, including scleroderma (23–26), rheumatoid arthritis (27), and undifferentiated connective tissue disease (28), a chronic disease that shares clinical characteristics of SLE. A volatile organic solvent, trichloroethylene, has been linked with the presence of low-titer antinuclear antibodies (17,21). Experiments in lupus-prone mice have shown acceleration of disease and an increased prevalence of antinuclear and anti-DNA antibodies (specific for the diagnosis of SLE) in mice exposed to trichloroethylene and its metabolite dichloroacetyl chloride (29).

Genetic polymorphisms in the glutathione S-transferase (GST) superfamily of phase II xenobiotic biotransforming enzymes modulate pathways of glutathione conjugation of highly reactive metabolites for organic compounds. These pathways reduce reactivity and cytotoxicity of reactive metabolites and confer protection against oxidative stress and immunogenic alterations in cellular protein, RNA, and DNA. Individuals who are homozygous for GSTM1-null and GSTT1-null genes lack GSTM1 and GSTT1 enzyme activity; individuals who are homozygous for the GSTP1 105Val (GG) (rs1695) single-nucleotide polymorphism (SNP), which encodes a valine in the substrate-binding site at position 105, may have reduced GSTP1 glutathione conjugation efficiency with some but not all substrates (30–33).

Each of these polymorphisms may reduce glutathione conjugation, one of the body's protective mechanisms to modulate reactive metabolite–induced oxidative stress and DNA damage (34,35), a hypothesized risk factor for SLE. The GST genes catalyze metabolic pathways for detoxification of tobacco smoke. Homozygosity for GSTM1, GSTT1, or GSTP1*GG is associated with the risk of early-onset lung cancer (36–38). GST polymorphisms have been associated with clinical SLE manifestations but not with susceptibility to SLE (39). These functional polymorphisms vary by race and ethnicity (32,40–43). For example, the GSTM1-null polymorphism is more frequent in African Americans than in Caucasians (40). Thus, GST gene patterns in African Americans who are exposed to organic compounds that require GST enzymes for degradation and excretion may in part explain the earlier age at onset of SLE in this racial group (44).

Community concerns about a possible SLE "cluster" in 3 predominantly African American Boston neighborhoods (Roxbury, Dorchester, and Mattapan) that contained >400 Massachusetts Department of Environmental Protection 21E hazardous waste sites led us to investigate a possible environmental trigger of SLE in this area. These neighborhoods have 228,204 residents and comprise 32 km^2, with a population density of ~7,100/km^2. The ethnic distribution is 75% African American, 15% Hispanic, 5% Caucasian, and 5% other or not specified, and the population has extraordinary economic and health disparities (www.bphc.org). The Roxbury Lupus Project was a collaboration among 6 Boston hospitals, a neighborhood-based lupus support group (Women of Courage), and the Massachusetts Department of Public Health (DPH). The goals of the Roxbury Lupus Project were to determine the prevalence of SLE in the study area and to investigate potential associations of environmental exposures, based on residential proximity to reported hazardous waste sites, and GST gene patterns with SLE. We hypothesized that residential exposure to petrochemicals may increase the risk of SLE in this population.

PATIENTS AND METHODS

Study population. Eligible SLE patients were women with a current address within the target zip codes that corresponded to 3 Boston neighborhoods (Roxbury, Dorchester, and Mattapan). The Brigham and Women's Hospital Lupus Registry, which dates back to 1992, was expanded for this study to include SLE patients from the study region who were seen at other Boston area hospitals. The Boston Lupus Registry contains data on 1,412 patients identified through the inpatient and outpatient billing databases of 5 major urban medical centers and 1 local community hospital in Boston. We validated the choice of hospitals by studying the DPH hospital discharge database, which includes inpatient data from 1999 to 2000 for all Massachusetts hospitals. Ninety-one percent of all

SLE admissions occurred at 1 of the 6 hospitals included in this study, and 9% occurred at 1 of 7 community hospitals in the greater Boston area. Thus, the majority of SLE patients with zip codes from the study area were admitted to 1 of the 6 study hospitals.

Trained study rheumatologists reviewed medical records to confirm the diagnosis of SLE and the date of clinical diagnosis, according to American College of Rheumatology classification criteria (45,46). One hundred ninety-one eligible patients were identified from the Registry. We also implemented an 18-month educational community outreach program to increase awareness about SLE in the community. The educational outreach program, efforts of the Women of Courage support group and the DPH, and recruitment efforts of Boston area rheumatologists resulted in additional self-referral of potential SLE patients (n = 35), who all gave permission for examination of their medical records; the diagnosis of SLE was confirmed in 18 of these women by medical record review. A total of 209 eligible patients with SLE were identified from the study region through the Registry and outreach program. We mailed up to 3 letters describing the study to these women and telephoned the nonrespondents. We were unable to contact 14 (7%), 58 (28%) were nonrespondents, and 137 (65%) responded. Of the respondents, 99 patients with SLE participated in the study, and 38 chose not to participate. The participation rate of 47% among a predominantly African American population is similar to that in other studies using similar recruitment methods (47).

The community outreach team received training in lupus information and interview methods to obtain demographic data and residential and occupational histories and to administer the Connective Tissue Disease Screening Questionnaire (48,49). Enrollment in the Roxbury Lupus Project began in April 2002 and ended in August 2003. Race and ethnicity were determined by self-report, according to the categories defined for use in the 2000 US Census (www.census.gov). The study protocol was approved by the institutional review boards of all participating institutions. All participants gave informed consent for interviews, blood sample collection, and genetic testing.

Exposure assessment. Data on demographic factors and complete residential history were obtained by structured interview. The residential history included the location (street address or nearest intersection or landmark) of all residences at which a participant lived for ≥12 months, starting at age 15 years. We chose not to collect data on childhood residence because the exposure database did not have information from the years prior to 1982, when many of the SLE patients were children. Environmental exposures were assessed with a questionnaire from the Systemic Lupus Erythematosus Risk Factor Questionnaire used in the Carolina Lupus Study (22,50–52), which was adapted for an urban population and and modified according to recommendations of the Women of Courage and other community partners.

Residential addresses and hazardous waste site addresses were geocoded using ArcView version 8 software. The longitude and latitude coordinates were projected using the Massachusetts State Plane Coordinates System. Missing and unmatched addresses were investigated by telephone calls to participants to ask for a specific house number, street address, and nearby landmarks. We also consulted old street maps located at Boston City Hall and traveled to neighborhoods, using hand-held GPS devices to obtain the latitude and longitude coordinates of reported landmarks and addresses.

Identifying hazardous waste sites. Under the General Laws of Massachusetts Chapter 21E, the Massachusetts Department of Environmental Protection has the authority to take all action appropriate to ensure that the Commonwealth complies with federal environmental legislation. As part of this authority, the Department of Environmental Protection identifies hazardous waste sites, defined as sites where oil or hazardous material has been deposited, stored, disposed of, or placed, and maintains information about these sites in a database. These hazardous waste sites are also known as 21E sites. Although the information compiled is not uniform nor was it collected for health-related purposes, it contains limited data on the types and amounts of chemicals at a site at the time that the site was reported. The database also contains limited information about followup site inspections, the type of remediation action that is required by law based on the level of risk at the site, and the date of remediation.

For this study, we identified 21E sites within the study census tracts in Roxbury, Dorchester, and Mattapan, Massachusetts by accessing the information in the database from the Department of Environmental Protection Web site (www.state.ma.us/dep/bwsc/sitelist.htm). At the time of analysis, the Web site data covered 21E sites that had been identified between 1993 and 2002. As a result, staff from the Department of Public Health worked closely with staff from the Department of Environmental Protection to obtain information on sites that were identified between 1982 and 1993. Any site that was remediated within 1 year of being identified was excluded from the analyses, since we were interested in the effects of prolonged (>1 year) exposures on the age at diagnosis of SLE.

The information sought on sites included the unique site identification number, the types of chemicals found at the site, the amount or concentration of chemicals and the media (e.g., air, water, or soil) that were contaminated, the date the site was reported, the address or location of the site, the site compliance status including the date of any remediation activities, and the site's tier classification. The Tier Classification System is used by the Department of Environmental Protection to rank sites based on a numerical ranking system. Each site is scored on a point system based on a variety of factors, including the site's complexity, the type of contamination, and the potential for human exposure or environmental exposure to the contamination. Part of the process of ranking the 21E sites involves an assessment of potential exposure pathways. A total of 416 21E sites were identified in the study neighborhoods, and numerical ranking system information was available on 117 of them. Of these, 67 sites had additional information on potential exposure pathways such as air, water, or soil. We performed a subset analysis limited to these 67 sites, for which the most comprehensive information was available.

Genotyping. Genomic DNA was extracted from buffy coats in EDTA-preserved blood, using Qiagen (Chatsworth, CA) spin columns. Genotyping for GSTM1-null homozygosity, GSTT1-null homozygosity, and the GSTP1 105Val (GG) SNP was performed according to our previously published methods (43).

Statistical analysis. Case-only time-to-event analyses, in which the outcome of interest was the age at SLE diagnosis (or equivalently, time to SLE diagnosis) were conducted. This analytical technique was used to test whether increased exposure to hazardous waste sites or chemical releases over time was associated with an earlier age at diagnosis of SLE. The effect of exposure can be detected in a case-only analysis as follows. For a patient in whom SLE was diagnosed at age 35 years, the analysis compares exposure up to age 35 years with the exposures, also up to age 35 years, of all other patients who were diagnosed after age 35 years. If exposure truly accelerates the time to diagnosis, the patient diagnosed at age 35 years would be expected to have had higher exposure than the individuals not diagnosed by that age.

Cox proportional hazards models were used to study the association of residential proximity to hazardous waste sites over time (adjusting by stratification for date of birth in 11 categories) on the hazard of earlier lupus diagnosis (53). To account for changing residential exposures over time, latitude and longitude coordinates from geocoding were included as time-dependent variables in the Cox models. The case-only Cox model provides a valid test of the null hypothesis that there is no association between covariates and age at diagnosis. A P value of less than 0.05 for a covariate in the Cox models can be interpreted as evidence that the corresponding covariate is associated with age at diagnosis of SLE. Hazard ratios can be interpreted as the relative risk of earlier diagnosis of SLE per 1-unit change in proximity measure.

Exposure of an individual at time t was modeled 2 ways: 1) as proximity to active sites (1/distance between site and residence at time t, added over all active sites at time t), or 2) as the number of sites active at time t and within 1 km of the subject's residence at time t. Both models assume that the effect is additive across sites. In the first model, 2 sites located at the same distance from a residence have the same effect as a single site at half that distance from the residence; in the second model, all sites within 1 km of the residence have the same effect on age at diagnosis of SLE when compared with all sites beyond 1 km from the residence. These measures of exposure change over time as people change residences and sites are reported and remediated at different locations.

Homozygosity for GSTM1-null, homozygosity for GSTT1-null, and the presence of GSTP1 GG were studied as independent predictors of hazard of SLE diagnosis in Cox models adjusted for date of birth, using each polymorphism as an independent predictor, and a single composite variable for altered GST enzyme function encoded by any one of these genes (36–38,54). We did not consider haplotype analysis since the GST genes are on different chromosomes; GSTM1 is on chromosome 1, GSTT1 is on chromosome 22, and GSTP1 is on chromosome 11. We considered effect modification of exposure by genotype using a multiplicative interaction term between exposure and each genotype, and between exposure and combinations of genotypes.

Despite the lack of uniform and comprehensive chemical and exposure information for all of the sites, analyses were first conducted using all 416 sites. Subset analyses were also performed by grouping sites in several different ways, based on the available information. Sites were categorized on the basis of the presence of 63 petroleum-related chemicals, and each chemical was classified based on its tendency to volatilize and its relative rate of biodegradation and mobility in the media in which it was measured. Grouping criteria included presence of petrochemicals, presence of volatile petrochemicals, and sites with additional exposure pathway information. Additional grouping criteria were based on combinations of the above site features. The objective in grouping sites was to increase the power to detect possible true effects, although it is important to note that information recorded in the database is recorded at the time when the site is reported, not after the site is inspected.

Sixty-seven sites were selected for subset analysis, based on the presence of additional information on potential exposure pathways. Although we were not able to discern why these particular sites had more detailed information, we investigated whether there was a population density–related bias regarding collection of information on these sites, by testing whether the average population density for census tracts containing these 67 sites was significantly different from what one would expect if the 67 sites were a random sample of all 21E sites. There was no significant association of the 67 sites with either the density of the African American population ($P = 0.2$) or the total population density ($P = 0.6$) (year 2000 US census). Sites with exposure pathway information were twice as likely to have ambient air tested for contaminants compared with sites without pathway information ($P = 0.006$). However, among sites with ambient air testing, there was no association between measured concentration amounts and the presence of pathway information ($P = 0.6$ by the Wilcoxon test). Although information on chemical contaminants present at a site was not always complete, an exploratory analysis of the 67 sites suggested that these sites also tended to be contaminated with volatile organic compounds ($P < 0.0001$), diesel fuel ($P = 0.02$), gasoline ($P = 0.03$), benz(A)anthracene ($P = 0.04$), unknown hazardous material ($P = 0.02$), and unknown chemicals ($P = 0.003$) more often than other sites. However, only contamination with volatile organic compounds was significant (at the global level, $\alpha = 0.05$) when a Bonferroni correction was applied. As a result, a subset of analyses limiting the data to these 67 sites were conducted to test the hypothesis of higher potential risk of exposure to volatile organic compounds from these sites.

RESULTS

A total of 416 unique hazardous waste sites were identified in the Department of Environmental Protection database. Analysis of the chemical contamination showed that 57% of the sites had some contamination

Table 1. Frequency of petrochemicals in 416 21E hazardous waste sites in Roxbury, Dorchester, and Mattapan, Massachusetts

Type of chemical	No. (%) of sites
Identified petrochemicals	238 (57)
All petrochemicals volatile	88 (21)
Some petrochemicals volatile, some not	49 (12)
Reported petrochemicals, none volatile	101 (24)
No petrochemicals among identified chemicals	80 (19)
No identified chemicals	98 (24)

with petrochemical compounds, and of this group 58% included volatile petrochemical contaminants (Table 1).

Of the 209 patients with confirmed SLE who resided in the study region, 99 women (47%) were enrolled in the Roxbury Lupus Project. Based on the total number of adult women (age ≥18 years) in the study region from US census data (N = 88,210), the overall prevalence of SLE is 2.37 cases per 1,000. If we assume that the ethnic distribution in the 209 cases identified is the same as the distribution in our study participants (167 [80%] with African heritage) and that all 167 women lived in the study region in the year 2000, and use 2000 US census data on the number of adult (age ≥18 years) African American women in the study region (N = 46,969), then the prevalence of SLE among African American women in these neighborhoods is 3.56 SLE cases per 1,000. After excluding 6 subjects who lived outside the area prior to SLE diagnosis, 93 SLE patients, with dates of diagnosis ranging from 1960 to 2003 (median 1996), and ages at diagnosis ranging from 15 to 74 years (median 34 years), of whom 80% had African heritage, were included in the analysis. Of 93 SLE patients, 58 (62%) had ≥1 altered GST genotype (Table 2).

All-site and subset analyses. We considered many different models, based on 11 different ways of subsetting the sites, and several ways of classifying combinations of GST gene abnormalities; among these analyses, a few produced significant results. Proximity to sites was not associated with the risk of earlier SLE diagnosis, using data on all 416 sites ($P > 0.05$ for each of the proximity measures in all models) (Table 3) or in analyses limited to the 67 hazardous waste sites for which exposure pathway information was available (Table 4). In exploratory analyses, we also investigated lagged measures at 3 and 5 years and integrated measures of exposure. None of these covariates was individually significant at the 5% level (data not shown). The combination of homozygosity for GSTM1-null and the presence of GSTP1 GG was associated with an earlier age at diagnosis when adjusted for either proximity measure ($P = 0.03$) in the analysis of all 416 sites (Table 3) and in analyses of the subset of 67 sites with exposure pathway information (Table 4). Results for the genotype associations were similar in the analyses using proximity defined as the number of active sites within 1 km among these 67 sites (data not shown). When we limited the analyses to non-Caucasian subjects, the results were essentially unchanged.

Interaction analyses. We considered each genotype independently in an interaction model with proximity defined either as 1/distance or as number of active sites within 1 km, but no individual loci showed significant interactions with proximity. There were no significant interactions of combinations of loci with proximity to the 416 sites (data not shown). In an analysis of the 67 sites with exposure pathway information, a covariate indicating an altered genotype for ≥1 GST gene had a significant interaction effect with proximity to sites

Table 2. Demographic characteristics and GST genotyping of the Roxbury Lupus Project participants (n = 93 SLE patients)*

Age at diagnosis, years	
Mean	35.9
Median	34
Range	15–74
Date of diagnosis, median	March 1996
Age at interview, mean ± SD years	44.3 ± 13.8
Time from diagnosis to study interview, years	
Mean	8.4
Range	0–42
Education, mean ± SD years†	14.2 ± 3.2
Employed full- or part-time, no. (%)†	44 (47.3)
Race/ethnicity, no. (%)‡	
Hispanic	9 (10)
African American	1 (1)
Not specified	8 (9)
Non-Hispanic	84 (90)
African American	63 (68)
West Indian/Caribbean/African descent	11 (12)
Caucasian	6 (6)
Other	2 (2)
Unknown	2 (2)
GSTM1, GSTT1, and GSTP1 105Val (GG) genotypes, no. (%)	
GSTM1-null homozygous	38 (41)
GSTT1-null homozygous	26 (28)
GSTP1 (GG)	15 (16)
≥1 altered GST allele	58 (62)
GSTT1-null, GSTM1-null, GSTP1 (GG)	2 (2)

* GST = glutathione S-transferase; SLE = systemic lupus erythematosus.
† At time of study interview.
‡ There were no Asians, Pacific Islanders, American Indians, or Alaskan natives.

Table 3. GST genotypes, combinations of genotypes, and residential proximity to all 21E hazardous waste sites (total of 416) in the Roxbury, Dorchester, and Mattapan neighborhoods of Boston, Massachusetts, and hazard of SLE diagnosis*

	Proximity defined as 1/distance from residence to sites			Proximity defined as number of sites within 1 km of residence		
Cox models†	Hazard ratio‡	95% CI	*P*	Hazard ratio	95% CI	*P*
Model 1						
GSTM1-null (n = 38)	1.27	0.73–2.21	0.41	1.29	0.74–2.25	0.37
Proximity	0.98	0.89–1.10	0.78	0.98	0.93–1.03	0.41
Model 2						
GSTT1-null (n = 26)	1.20	0.66–2.20	0.55	1.20	0.66–2.18	0.55
Proximity	0.99	0.89–1.10	0.87	0.98	0.93–1.03	0.47
Model 3						
GSTP1 GG (n = 15)	1.37	0.65–2.91	0.41	1.36	0.64–2.88	0.42
Proximity	0.99	0.89–1.10	0.87	0.98	0.93–1.03	0.48
Model 4						
Any altered GST allele (n = 58)	0.73	0.42–1.27	0.27	0.73	0.42–1.26	0.25
Proximity	0.99	0.89–1.10	0.83	0.98	0.93–1.03	0.43
Model 5						
GSTM1-null and GSTP1 GG (n = 53)	3.40	1.13–10.26	0.03	3.46	1.14–10.47	0.03
Proximity	0.98	0.88–1.10	0.78	0.98	0.93–1.03	0.42
Model 6						
GSTM1-null and GSTT1-null (n = 64)	0.85	0.37–1.95	0.70	0.83	0.36–1.91	0.66
Proximity	0.99	0.89–1.10	0.79	0.98	0.93–1.03	0.44
Model 7						
GSTT1-null and GSTP1 GG (n = 41)	1.07	0.29–4.04	0.92	1.03	0.27–3.90	0.96
Proximity	0.99	0.89–1.10	0.80	0.98	0.93–1.03	0.46

* GST = glutathione S-transferase; 95% CI = 95% confidence interval.
† Cox proportional hazards models predicting age at diagnosis of systemic lupus erythematosus (SLE) adjusted for age, altered allele or combination of alleles, and proximity.
‡ Hazard ratios can be interpreted as the relative risk of earlier diagnosis of SLE per 1-unit change in proximity measure.

defined as 1/distance ($P = 0.03$) and a significant interaction with proximity defined as number of active sites within 1 km ($P = 0.02$) (Table 5). Since the interaction term was significant in these models, the effect of an additional site was significantly different for individuals with no altered GST genes compared with those with ≥1 altered GST gene. However, the estimated risk of earlier age at SLE diagnosis was not significantly higher among individuals with an altered GST gene compared with those with normal genotypes, unless ≥5 hazardous waste sites were present within 1 km of residence. For example, when 5 hazardous waste sites were within 1 km of residence, the hazard ratio associated with the presence of any altered GST gene was 12.5 (95% confidence interval 1.02–152). Significant interactions were identified when the following genotypes were considered: homozygous GSTM1-null or GSTP1 GG ($P = 0.02$ for interaction with proximity as 1/distance and $P = 0.02$ for interaction with proximity within 1 km); and homozygous GSTM1-null or homozygous GSTT1-null ($P = 0.03$ for interaction with proximity as 1/distance and $P = 0.02$ for interaction with proximity within 1 km). No other combinations of genotypes demonstrated significant interaction. Analyses limited to non-Caucasian subjects yielded similar results.

DISCUSSION

Epidemiologic studies in the US over more than 2 decades have consistently shown significant differences in the predisposition to SLE in African Americans and Caucasians. In each investigation, SLE has been shown to occur in African Americans at least 3 times more often than in Caucasians (1–6). Since African Americans tend to live in urban environments with more potential exposure to volatile petrochemicals, petrochemical exposure might explain the observed prevalence differences. Neighborhood data from Massachusetts and across the nation document disproportionately higher exposure to hazardous waste among African Americans (55–58). Although the prevalence of 3.56 cases per 1,000 among African American women in this group is within the reported range of 0.18–4 cases per 1,000 (1–6), we

Table 4. GST genotypes, combinations of genotypes, and residential proximity defined as 1/distance to a subset of 21E hazardous waste sites (total of 67) in the Roxbury, Dorchester, and Mattapan neighborhoods of Boston, Massachusetts, and hazard of SLE diagnosis*

Cox models†	Hazard ratio‡	95% CI	*P*
Model 1			
GSTM1-null (n = 38)	1.26	0.72–2.20	0.42
Proximity	1.04	0.60–1.79	0.89
Model 2			
GSTT1-null (n = 26)	1.21	0.67–2.20	0.53
Proximity	1.06	0.62–1.81	0.83
Model 3			
GSTP1 GG (n = 15)	1.40	0.66–2.96	0.38
Proximity	1.09	0.63–1.87	0.77
Model 4			
Any altered GST allele (n = 58)	0.73	0.42–1.27	0.27
Proximity	1.04	0.60–1.78	0.90
Model 5			
GSTM1-null and GSTP1 GG (n = 53)	3.40	1.13–10.23	0.03
Proximity	1.06	0.62–1.82	0.82
Model 6			
GSTM1-null and GSTT1-null (n = 64)	0.86	0.37–1.98	0.72
Proximity	1.05	0.61–1.80	0.87
Model 7			
GSTT1-null and GSTP1 GG (n = 41)	1.06	0.28–4.00	0.93
Proximity	1.06	0.62–1.82	0.84

* See Table 3 for definitions.
† Cox proportional hazards models predicting age at diagnosis of SLE adjusted for age, altered allele or combination of alleles, and proximity.
‡ Hazard ratios can be interpreted as the relative risk of earlier diagnosis of SLE per 1-unit change in proximity measure.

were unable to demonstrate any association between exposure to hazardous waste sites and risk of SLE in the largely African American population.

We analyzed the effect of proximity to 21E hazardous waste sites in 3 urban Boston neighborhoods on age at diagnosis in 93 SLE patients, 80% of whom had African heritage. In the all-site analysis, we found no significant association between proximity to sites and the risk of earlier SLE diagnosis. The combination of homozygosity for GSTM1-null and GSTP1 GG was associated with an earlier SLE diagnosis, when adjusted for proximity to hazardous waste sites. However, associations of each of the 3 individual GST genotypes, other pairwise genotype combinations, and gene–environment associations (GST genotype and residential proximity to hazardous waste sites) and risk of earlier SLE diagnosis were not significant in the all-site analysis.

In our analysis of a restricted number of sites with available exposure information, we found modest evidence of a statistically significantly increased risk of

Table 5. Gene–environment interactions between GST genotypes and residential proximity to a subset of 21E hazardous waste sites (total of 67) in the Roxbury, Dorchester, and Mattapan neighborhoods of Boston, Massachusetts*

Interaction term in Cox model†	*P* (proximity defined as 1/distance)	*P* (proximity defined as number of sites within 1 km)
Any altered GST allele X proximity	0.03	0.02
GSTM1-null or GSTP1 GG X proximity	0.02	0.02
GSTM1-null or GSTT1-null X proximity	0.03	0.02
GSTT1-null or GSTP1 GG X proximity	0.49	0.23

* See Table 3 for definitions.
† Cox proportional hazards models predicting age at diagnosis of SLE adjusted for age, altered allele, proximity, and interaction term (altered allele * proximity).

earlier SLE diagnosis in patients who lived close to the 67 hazardous waste sites evaluated and had alterations in any 1 of 3 genotypes associated with altered GST enzyme function (homozygous GSTM1-null, homozygous GSTT1-null, or GSTP1 GG). The 67 sites in this subset analysis were significantly more likely to be contaminated with volatile organic compounds compared with the other sites.

The GST superfamily of enzymes includes ≥7 family members that control the breakdown of highly reactive metabolites for broad classes of organic compounds that include aromatic hydrocarbons and organochlorine pesticides such as DDT, petroleum by-products, and dioxin (34,59–63). The reactive metabolites of these compounds are carcinogenic (64–66). GST enzymes are involved in mechanisms that protect against damage to DNA (67,68). Among the GST enzyme superfamily, disease associations with functional variation of 3 members (GSTM1, GSTT1, and GSTP1) have been studied extensively. The GSTP1*Ile105Val SNP and GSTM1-null and GSTT1-null genes are common, occurring in 20–25% of African Americans (69–71). GST genes also catalyze metabolic pathways for detoxification of reactive oxygen compounds that may be generated by ultraviolet radiation in sunlight. European Americans with the GSTM1-null homozygous genotype and long-term occupational sun exposure have a 3-fold higher risk of SLE than controls, with a statistically significant interaction between genotype and sun exposure ($P = 0.03$) (43). Similarly, our observation of significant gene–environment interaction between GST genotypes and proximity to a subset of hazardous waste sites on the risk of earlier SLE diagnosis suggests that the GST enzymes may be particularly important in the detoxification of organic compounds.

We studied gene–environment interactions using case-only analysis and Cox proportional hazards models. The study was initially planned as a case–control study; however, valid case–control analysis would require that controls be drawn from the appropriate reference distribution of residential histories, a complicated and unverifiable assumption. Statistical analyses suggested that our control sample was not representative of the population distribution within the 3 communities for the year 2000. We compared the distribution of addresses reported for the year 2000 among the 204 controls recruited for this study with the 2000 US census distribution of African American women in the study census tracts (72,73). The distribution of addresses for controls in the year 2000 was significantly different from the population distribution recorded in the 2000 census (74).

This complex study has some limitations. We performed many analyses, only a few of which showed significant results. Thus, findings should be interpreted with caution due to the small sample size and modest statistical significance. The study was limited to SLE patients who were alive in 2002. It is possible that in patients who had died of their disease, and were therefore not included in the study, SLE was related to the hazardous waste sites and/or GST genes. Consequently, the study may have included only SLE patients who were not affected by proximity to hazardous waste sites and so were able to survive longer with the disease than were their susceptible counterparts.

There is very little toxicologic information in the literature on the relationship between exposure to each individual "petroleum distillate" and the risk of developing SLE, and most of the available information is based on occupational exposures (28). We have analyzed occupational risk factors for SLE in this study and demonstrated an increased risk from silica exposure (75). The Department of Environmental Protection database does not contain detailed, uniform, comprehensive chemical and exposure information on all 416 sites, and more complete information on potential and completed exposure pathways was available for only 67 of the sites (16%). Therefore, additional individual site features may have an impact on exposure.

Additionally, the exposure pathway itself is uncertain. Due to the relatively shallow depth of groundwater in Roxbury, Dorchester, and Mattapan, any groundwater contamination in these areas has the potential to impact indoor air quality (76). Importantly, information on residential sources of petrochemicals from household cleaners was not available. Finally, we do not have information on residential exposures or demographic features of nonparticipants; such information would allow assessment for differences between participants and nonparticipants.

A significant strength of our study is the use of a novel analytical approach using case-only analysis to investigate environmental, genetic, and gene–environment interactions as predictors of a quantitative trait, age at diagnosis of SLE. The advantage of the case-only analysis is that it provides a valid test for an association between exposure and age at diagnosis. To our knowledge, only 2 rheumatoid arthritis studies have used case-only gene–environment interaction analysis (77,78). No similar studies on SLE have been published.

In summary, we hypothesized that the genes that control the production of several GST enzymes may have a central role in modulating the increased predisposition to SLE among urban African American women. In an analysis of a subset of hazardous waste sites, we found some evidence that SLE occurs at an earlier age in women who are GSTM1-deficient, have altered GSTP1 substrate-binding sites, and live near hazardous waste sites. In contrast, no increased risk of earlier onset of SLE was observed when we examined hazardous waste exposure or GST genotypes independently. Because of the number of analyses performed, our findings should be considered with caution but warrant further study. The Massachusetts Department of Public Health is working toward the development of systematic reporting of all SLE diagnoses for the City of Boston. Once the new registry is complete, more comprehensive evaluation of the hypotheses generated in this investigation will be possible.

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AUTHOR CONTRIBUTIONS

Dr. Karlson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Drs. Karlson, Cooper, McAlindon, Massarotti, Jajoo, Husni, and Knorr, Ms Condon, and Dr. Fraser.

Acquisition of data. Ms Watts, Drs. Wright, Costenbader, Massarotti, Fitzgerald, Jajoo, and Husni, Ms Fossel, Ms Pankey, and Ms Ding.

Analysis and interpretation of data. Dr. Karlson, Ms Watts, Mr. Signorovitch, Drs. Bonetti, Cooper, McAlindon, Costenbader, and Massarotti, Ms Pankey, Dr. Knorr, Ms Condon, and Dr. Fraser.

Manuscript preparation. Dr. Karlson, Ms Watts, Drs. Bonetti, Cooper, Costenbader, Husni, and Knorr, Ms Condon, and Dr. Fraser.

Statistical analysis. Dr. Karlson, Mr. Signorovitch, and Dr. Bonetti.

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