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Association of the G-463A Myeloperoxidase Gene Polymorphism with Renal Disease in African Americans with Systemic Lupus Erythematosus

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Abstract

Objective—Myeloperoxidase (MPO) is an enzyme expressed in neutrophils that is involved in tissue damage in inflammatory renal diseases. A functional G to A single-nucleotide polymorphism (SNP) is present at position −463 of the MPO promoter region and is associated with altered MPO expression. We hypothesized that the G-463A MPO SNP is a risk factor for developing lupus nephritis (LN) due to its potential influence on the inflammatory response.

Methods—DNA from 229 patients with SLE and 277 controls from the Carolina Lupus cohort, 58 African American patients from the Sea Island Lupus Cohort, and 51 African American patients from the Lupus Multiplex Registry and Repository were genotyped by PCR. A linear regression model was used to examine relationships between the MPO genotype, case/control status, demographic characteristics, and LN.

Results—There was no association of MPO genotype with systemic lupus erythematosus (SLE). However, the odds of developing LN were significantly higher among those with an A allele, compared to those without, in African American cases of all 3 cohorts. When the likelihood of developing LN was compared across MPO genotypes, the risk of developing LN was significantly higher among cases with a GA genotype versus GG (OR 2.11, 95% CI 1.12 to 3.97) and even higher with AA versus GG (OR 3.52, 95% CI 1.41 to 8.77).

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Conclusion—While the G-463A MPO SNP is not a risk factor for developing SLE, the low expressing A allele is a significant risk factor for developing LN that is gene dosage-dependent in African Americans. (First Release Sept 15 2007; J Rheumatol 2007;34:2028–34)

Keywords

SYSTEMIC LUPUS ERYTHEMATOSUS; AFRICAN AMERICAN; MYELOPEROXIDASE; POLYMORPHISM; LUPUS NEPHRITIS

Myeloperoxidase (MPO) is an heme enzyme abundant in neutrophils, monocytes, and macrophages. MPO plays a key role in the innate immune system as a microbicidal agent[1]. Activation of MPO leads to the production of hypochlorous acid (HOCl), a toxic oxidant that compromises DNA repair and mononuclear cell responsiveness *in vitro*[2]. The MPO-H_2O_2 system can also generate reactive nitrogen species and tyrosyl radicals depending on the cellular milieu[3]. The inappropriate release of MPO and its reactive byproducts at an inflammatory site may result in tissue damage and organ dys-function[4]. Alternatively, MPO can also be antiinflammatory in specific biologic settings. A yin and yang relationship between nitric oxide (NO) and HOCl is proposed such that HOCl, when produced along with NO, can serve to sequester NO and prevent its deleterious effects[3]. The products of MPO and NO synthases (NOS) modulate the activity of each other. NO at low levels increases the activity of MPO, while at high levels it inhibits its activity[5]. MPO can act as a catalytic sink for NO, a process that can limit the levels of NO in an inflammatory reaction[6]. Byproducts of MPO expression can also be antiinflammatory by blocking specific cytokine and chemokine production including monocyte chemoattractant protein 1 (MCP1)[7]. MPO was shown in various animal models to be a pathogenic factor in kidney disease, although it is the overproduction of MPO that is pathogenic in these animal models[3]. As NO is a known modulator of lupus nephritis, polymorphisms that influence MPO expression, depending on the biologic milieu, could either enhance or diminish development of lupus and/or lupus nephritis (LN).

The MPO gene extends over 14 kilobases on chromosome 17q21-23. Austin, *et al*[8] reported a single-nucleotide polymorphism (SNP) involving a guanine to adenosine transition in the promoter region at position −463 relative to exon 1. This polymorphism lies within an Alu repeat. Kumar, *et al* reported that PPAR-γ (peroxisome proliferators-activated receptor gamma) binds the Alu repeat, inducing MPO in the presence of macrophage colony-stimulating factor (MCSF) while suppressing MPO in the presence of granulocyte/ macrophage colony-stimulating factor (GM-CSF). The estrogen receptor binds −463 A preferentially, and estrogen blocks PPAR-γ actions, especially on the MPO A allele[9]. Hoy, *et al* found that circulating levels of MPO are not affected by the G-463A SNP in healthy individuals[10]. Rutgers, *et al* also found that neutrophil MPO activity and protein levels were not different between 463 GA genotypes in healthy individuals[11]. In contrast, Van Schooten, *et al* found that the A allele is associated with a reduced MPO activity per neutrophil in bronchoalveolar lavage fluid of tobacco smokers[12], which suggests that the polymorphism may affect MPO expression differentially in inflammatory conditions. Thus the influence of the polymorphism on MPO expression *in vitro* varies with culture conditions and the influence *in vivo* is unclear.

Systemic lupus erythematosus (SLE) is a complex multi-factorial autoimmune disease characterized by autoantibody production and immune complex deposition, leading to intense inflammation and end-organ damage[13,14]. Although the pathogenesis of SLE is multifactorial, the inflammatory expression of SLE, particularly during periods of exacerbation, implies that a state of oxidative stress may exist[15]. Despite improved survival in patients with SLE recently, lupus nephritis remains a leading cause of morbidity and mortality[16]. Multiple factors are implicated in the development of LN, including the type of immunological trigger, severity of

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tissue inflammation, systemic and local hemodynamic factors, treatment course and genetic-hereditary load[17]. The colocalization of MPO and HOCl-modified proteins at the glomerular basement membrane in human membranous glomerulonephritis, the presence of HOCl-modified proteins in mononuclear cells of the renal interstitium and in damaged human tubular epithelia, and the inflammation induced and exacerbated by MPO antibody complexes in necrotizing glomerulonephritis all support MPO being an important pathogenic factor in glomerular and tubulointerstitial diseases[3,18-21]. It is possible that subtle changes, like polymorphisms in genes of immune function, that have little or no effect in the general population, assume a greater significance in individuals with defects in host defense systems, such as SLE. In this setting, one would predict that the coinheritance of susceptibility genes may influence the development and severity of SLE and LN. We hypothesized that the G-463A MPO SNP may be a risk factor for developing lupus nephritis (LN) due to its potential modulatory effects on MPO expression.

MATERIALS AND METHODS

Study populations

Subjects for the initial phase of this study were enrolled in the Carolina Lupus (CLU) Study, a case-control inception cohort study of genetic and environmental factors predisposing to SLE[22]. Only African American and Caucasian individuals were used from the CLU cohort, as there were insufficient numbers of other racial/ethnic groups for any valid statistical comparisons. The 229 SLE patients resided in eastern North Carolina and South Carolina for at least 6 months prior to diagnosis and met the 1997 revised American College of Rheumatology (ACR) classification criteria for SLE. They were all diagnosed between January 1, 1995, and July 31, 1999, and were enrolled within 1 year of diagnosis. The CLU study included 277 population-based age, sex, and geographic region frequency-matched controls that were randomly selected from state driver's license registries. Genomic DNA was extracted from blood samples obtained from SLE patients and controls at the time of enrollment. Confirmatory cohorts subsequently analyzed included the first 58 African American SLE cases enrolled in our Sea Island Lupus cohort[23] and 51 African American SLE cases randomly selected from the Lupus Multiplex Registry and Repository (LMRR)[24]. Increasing the sample size for SLE cases by including the other 2 cohorts substantially raised the statistical power (i.e., from 46% to 83%) for detecting differential odds of developing nephritis across the MPO genotypes. This study was approved by the Medical University of South Carolina, the Oklahoma Medical Research Foundation, and the University of Oklahoma Institutional Review Boards. Within each of these 3 cohorts, LN was defined as having biopsy-confirmed Class III or IV lupus nephritis as defined by World Health Organization classification. Patients with an abnormal urinalysis, but no renal biopsy, were excluded from the analysis of association with renal disease.

Genotyping procedure

G-463A MPO gene mutations were characterized by polymerase chain reaction (PCR) analysis with modification of the method of London, *et al*[25].

Confirmation of polymorphism by direct sequencing

Amplified, undigested cDNA segments from randomly selected patients and controls were sequenced using an automated ABI DNA sequencer to confirm the presence of the polymorphism and the validity of the PCR procedure.

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Statistical analysis

Initially, analyses were performed only on the CLU cohort. Comparisons of demographic characteristics between cases and controls and of the frequency of LN between African American and Caucasian SLE cases were performed using chi-square tests or t-tests, as appropriate. Frequencies of the distribution of MPO genotypes were calculated and compared between cases and controls, and between cases with and those without LN. Statistical tests comparing the MPO genotype distribution between cases and controls were made using logistic regression models, stratified by race. Because of a relatively small number of Caucasian subjects who were homozygous for the A allele, the heterozygous GA genotype and homozygous AA genotype were collapsed into one category. The dichotomous case/control status indicator served as the dependent variable, with the A allele indicator being the primary independent variable of interest. These models also adjusted for gender, in effect allowing us to determine the independent effect of the presence of the A allele on the development of SLE. Similar models were constructed to determine whether MPO genotype (i.e., the presence of the A allele) was associated with the development of LN among SLE cases. Again, stratified analyses were performed for both race groups; however, the models included age, sex, and disease duration as covariates.

When the augmented dataset (i.e., that including data on African American cases from the 3 separate SLE cohorts) was analyzed, the focus was entirely on the association of MPO genotype and the presence of WHO Class III-IV LN. The dichotomous classification of presence or absence of LN served as the dependent variable in a logistic regression model, with MPO genotype serving as the primary independent variable of interest. There were insufficient numbers of Caucasian patients with lupus nephritis in the CLU cohort to derive any meaningful conclusions, so association of the MPO SNP with LN was tested only in African American subjects. Because these analyses included only African American subjects, and because there were sufficient numbers of subjects with each of the 3 genotype classifications (AA, GA, GG), the 3-group MPO classification variable was used. In addition to age, sex, and disease duration being included as covariates, a cohort classification variable was also included in the model, to account for the possibility of differential underlying LN rates by cohort.

RESULTS

Cohort demographics

Characteristics of the 3 different cohorts (CLU, Sea Island Lupus Cohort, and Lupus Multiplex Registry and Repository) are summarized in Table 1. All cases met the 1997 revised ACR classification criteria for SLE. Within the CLU cohort, the unrelated healthy controls were similar in age, sex, and geographic location to the lupus cases. The proportions of cases with LN were significantly higher in the Lupus Multiplex Registry (56.9%) and the Sea Island Lupus (39.7%) cohorts compared to African American cases in the CLU cohort (24.1%) ($p < 0.001$ and $p < 0.05$, respectively). This is likely secondary to the CLU being an inception cohort in contrast to the other 2 cohorts, which enrolled individuals regardless of disease duration. Cases in the Lupus Multiplex Registry were significantly ($p < 0.0001$) older (mean 47.0, SD 11.7 yrs) than African American cases from the CLU cohort (mean 40.3, SD 14.4 yrs). Disease duration was significantly ($p < 0.0001$) longer among cases in the Lupus Multiplex Registry (mean 7.6, SD 7.0 yrs) and Sea Island Lupus (mean 7.8, SD 6.8 yrs) cohorts than African American cases from the CLU cohort (mean 1.3, SD 0.9 yrs), as expected based on the recruitment strategies for the cohorts.

MPO genotype association with lupus

The distribution of MPO genotypes by relevant clinical and demographic subgroups within the 3 cohorts is given in Table 2 with several notable findings from the unadjusted analyses.

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The MPO A allele frequency was higher, but not statistically different, among the CLU cohort SLE cases compared to control subjects. In general, the A allele seemed to be more frequent among African American SLE cases (range among cohorts 49.7% to 62.1%) compared to Caucasian SLE cases (45.2% in the Caucasian CLU cohort). The genotype distribution (AA, GA, and GG) varied, but not significantly, across the 3 cohorts of African American SLE cases, allowing the 3 cohorts to be combined for analysis. All genotype analyses in all 3 cohorts fit the Hardy-Weinberg equation.

Results of the logistic regression models indicate that after adjusting for sex, the A allele was not significantly ($p = 0.141$) more likely to be present among Caucasian cases (45.2% had the A allele) than Caucasian controls (36.0% had the A allele); nor was the A allele significantly ($p = 0.989$) more likely to be present among African American cases (49.7% had the A allele) than African American controls (50.0% had the A allele). These findings suggest that the A allele is not a pre-disposing factor to SLE, although it is possible that by geno-typing more Caucasian cases and controls, a small genetic effect might be confirmed.

MPO genotype and lupus nephritis

After adjusting for sex, age, and disease duration in a logistic regression model limited to African American SLE cases within the CLU cohort, the odds of having LN was found to be significantly higher among those with the A allele present compared to those without the A allele (OR 2.36, 95% CI 1.03 to 5.42, $p = 0.043$). When the likelihood of having developed LN was compared across the 3 MPO genotypes, by including the African American SLE cases from all 3 cohorts in a multivariable logistic regression model, further association of the polymorphism with LN was found. After covariate adjustment, the likelihood of having LN was significantly ($p < 0.05$) higher among SLE cases with the GA genotype compared to the GG (OR 2.11, 95% CI 1.12 to 3.97) and even higher among SLE cases with the AA genotype compared to the GG (OR 3.52, 95% CI 1.41 to 8.77).

As pure Class V LN is not proliferative and likely differs pathogenetically from Class III and IV disease, we analyzed associations of the MPO polymorphism with the 2 LN subsets separately. When we analyzed LN Class V alone, there was still a strong, but not significant, association of the MPO polymorphism with Class V nephritis (GA vs GG: OR 1.37, 95% CI 0.56 to 3.34; and AA vs GG: OR 2.82, 95% CI 0.81 to 9.9). The association is significantly stronger, however, with Class III and IV nephritis (GA vs GG: OR 3.65, 95% CI 1.47 to 9.03; and AA vs GG: OR 3.92, 95% CI 1.18 to 13.03).

DISCUSSION

We examined the frequency of the G-463A MPO gene polymorphism in patients with SLE and matched controls and SLE patients with LN versus those without LN. To our knowledge, this is the first study to investigate the association between MPO polymorphisms and SLE/LN. Our results indicate that the G-463A MPO SNP is not significantly linked with development of lupus, but is highly significantly associated with development of proliferative nephritis in African American patients with lupus. The results were opposite to our preconceived hypothesis in that it was the A allele that was associated with lupus nephritis, in contrast to antineutrophil cytoplasmic antibody (ANCA) vasculitis that is associated with the G allele. The enhanced association of LN with individuals of the AA genotype versus GA versus GG genotype supports the significance of modulation of MPO expression in the pathogenesis of lupus nephritis in African Americans.

The etiology of SLE remains unknown, but is believed to be multifactorial, resulting from complex interactions between genetic, hormonal, immunologic, and environmental factors[13,14]. Practically, every compartment of the immune system has been reported to be abnormal in

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lupus[13,14]. However, the etiology of these abnormalities remains largely unresolved. Studies of animal models and recent human studies indicate a 2-phase pathogenesis in lupus. The first phase is the loss of tolerance leading to autoimmunity characterized by autoantibody production[26]. Both murine models and humans can progress to this stage of "lupus" without ever developing clinically significant signs or symptoms (i.e., first-degree relatives of lupus patients, sle1 mice and C3H/lpr mice)[26,27]. The second phase is the progression to end-organ involvement, with renal disease being the most serious and prevalent[26]. Genetic predispositions to the first phase (autoimmunity) are required for disease, but may not influence development of the second phase (autoimmune disease). The development of the first phase of disease on a "proinflammatory" genetic background, we propose, is crucial for development of end-organ involvement. As an example, we have previously reported an association of a SNP in the inducible nitric oxide synthase gene (iNOS), resulting in enhanced NO production, leads to a 3–4-fold increased risk of developing lupus in African American women[28].

Most polymorphisms are phenotypically benign in the normal host. However, in the appropriate environmental and genetic context, a polymorphism may influence susceptibility and/or outcome in a disease, often by acting upon one or more pathways unaffected by the primary defect[26]. Therefore, for a given population, polymorphisms may act as susceptibility genes and modify the clinical expression of the disease. Several SNP have been analyzed for linkage with the development of SLE and/or LN. Karassa, *et al* examined the role of the Fcγ-receptor IIa polymorphism in susceptibility to SLE and LN[29]. A metaanalysis of 17 studies, comparing 1405 patients with LN and 1709 without LN, concluded that the Fcγ-RIIa polymorphism represents a significant risk factor for SLE, but not for LN[29]. In another metaanalysis, Karassa, *et al* also found that the Fcγ-RIII A-V/F158 polymorphism has a statistically significant effect on the development of LN, but only a trend for the development of SLE[30]. These results are consistent with the 2-phase model of lupus disease development. Quintero-Del-Rio, *et al* found 2 SLE susceptibility loci, SLEN2 and SLEN3, in Black patients with SLE that are significantly associated with LN by linkage analysis. These loci were not associated with LN in White patients, emphasizing that ethnic differences likely exist in the genetics of SLE[24]. The identity of the genes responsible for this linkage effect remains unknown.

Interpretation of data on the potential role of this MPO gene polymorphism in the development of LN in African American patients with SLE is limited by the lack of published information on the functional significance of the polymorphism on MPO-mediated reactions relevant to autoimmune diseases. The *in vitro* data supporting the functional relevance of this polymorphism are strong[31]. The G to A base difference is located in the promoter region within an Alu repeat. PPAR-γ binds the Alu, inducing MPO when added with MCSF, while suppressing MPO when cultured with GMCSF in macrophages. The estrogen receptor alpha binds −463 A preferentially, and estrogen blocks PPAR-γ actions, especially on the MPO A allele with the stronger ER binding site. The MPO G allele, however, is not the higher expressing allele in all cell types and biologic settings. The GA genotype is associated with 1.6 to 2.5-fold higher MPO mRNA levels than GG in primary human peripheral blood mononuclear cells (PBMC). It is in macrophages that the GG genotype is associated with 4.6 to 7-fold higher MPO levels than GA[9]. Thus, the MPO A allele can be higher or lower expressing than the MPO G allele, depending on the cell type, inflammatory state, presence of PPAR-γ ligands, and estrogen levels[9]. In LN, the intrinsic immune cell, the mesangial cell, as well as infiltrating macrophages and neutrophils all can express MPO. Systemic or PBMC MPO expression may also not reflect the expression of MPO in the kidney.

Our studies of NO in lupus indicate that African American lupus patients produce significantly higher levels of NO than do Caucasians, and SNP in the iNOS gene are only linked with lupus in African Americans[28,32]. MPO has been shown to suppress the induction of iNOS gene expression due to consumption of low levels of NO required for iNOS induction[33]. These 2

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findings may partly provide a mechanistic explanation for the G-463A MPO polymorphism association with LN in African Americans in our analysis in that potentially low renal MPO expression may leave NO toxicity unopposed.

The G-463A MPO gene polymorphism is reported to be associated with susceptibility to several diseases including acute promyelocytic leukemia[8,34], multiple sclerosis[35,36], lung cancer[25], digestive tract cancer[37], Alzheimer disease[38-40], coronary artery disease[41,42], and MPO-ANCA-associated vasculitis in women[43]. Of interest, in most of these studies, it was the high producing G allele linked with disease[25,34,37,42-44]. In contrast, Mäkelä, *et al* found that GA/AA genotypes were associated with increased severity of atherosclerosis and larger aortic lesions than GG genotypes[45], and Reynolds, *et al*[39] found that in a Finnish population, the MPO A allele enhanced Alzheimer disease risk by 3.8-fold and also the MPO AA genotype was associated with selective mortality in men. Finally, Pope, *et al*[40] found that the AA allele was a risk factor for cognitive decline in a cohort of 2350 adults. These latter reports are consistent with our findings of an association of the A allele and LN.

The association of the apparent low producing MPO allele with development of LN in African American patients with lupus suggests that increased MPO expression is antiinflammatory and/or protective in LN. There are known mechanisms by which overexpression of MPO can be protective. Experiments in MPO-deficient mice indicate that T cell-mediated disease models are aggravated in MPO knockout mice, whereas more acute inflammatory models show protection in the MPO knockouts[36,46-49]. The MPO-hydrogen peroxide-chloride system can act as an antagonist to the NO/peroxynitrite pathway[3,4]. Further, MPO-derived chloramines have antiinflammatory effects. Taurine chloramines can inhibit cytokine production by leukocytes and impair and/or block expression of monocyte chemoattractant protein-1, free radical generation, and NO synthesis in macrophages[7]. In addition, the MPO-hydrogen peroxide-chloride system can down-regulate NADPH oxidase activity[3]. Conversely, NO, generated either by endothelial NOS at low concentrations or by iNOS at high concentrations, can inhibit MPO activity, albeit by different concentration-dependent mechanisms[3].

There are limitations to our study, including differences in the 3 cohorts studied. The CLU study is an inception cohort and thus individuals in this cohort may develop LN in the future[22]. We also included only patients with biopsy-proven Class III-V nephritis to insure only patients with LN were included. We excluded patients with abnormal urinalyses that had not had biopsies. The Lupus Multiplex Registry is a nationwide recruitment study to determine the genetics of lupus[24]. Again, only patients with biopsy-proven LN were included as LN. This cohort is older and has a higher prevalence of renal disease than the CLU cohort. Despite these differences, the association between LN and the MPO SNP was similar. The final cohort, the Sea Island cohort, comprised African Americans living on the Sea Islands of South Carolina. These individuals, referred to as “Gullah,” are highly genetically homogeneous with minimal genetic admixture, with common ancestral origin from Sierra Leone and the Ivory Coast[23]. The genetic homogeneity of this unique African American population offers advantages in defining genetic links with lupus and LN. The prevalence of the A allele is higher in the Gullah, although not significantly, than in the other 2 cohorts. The A allele, however, is significantly associated with LN in this cohort as in the other 2 cohorts. As with any association study, it is possible we are not studying the actual disease-associated polymorphism. Polymorphisms tend to be in linkage disequilibrium and thus the G-463A MPO polymorphism may not be pathogenic but in linkage dis-equilibrium with another SNP that is pathogenic. Formal analysis of linkage of SNP within the MPO promoter is not currently available.

In conclusion, studying the G-463A MPO gene polymorphism in SLE patients and controls, our results indicate that this SNP does not appear to be a risk factor for lupus, but the MPO A allele is significantly linked with developing proliferative LN in African Americans in a gene

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dose-dependent manner. Further studies will address whether the SNP is linked with progression of renal disease via followup of the CLU and Sea Island cohorts and the influence of this SNP on local expression of MPO in the lupus kidney. Finally defining the pathogenic role of MPO expression and its impact on lupus nephritis will allow better treatment and prevention strategies of the disease.

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Table 1

Demographic characteristics and lupus nephritis distribution for each of the 3 lupus cohorts.

Characteristics	Carolina Lupus		Lupus Multiplex Registry and Repository	Sea Island Lupus
	Cases, n = 229	**Controls, n = 277**	**Cases, n = 51**	**Cases, n = 58**
Female, n (%)	207 (90.4)	249 (89.9)	47 (92.2)	52 (89.7)
Male, n (%)	22 (9.6)	28 (10.1)	4 (7.8)	6 (10.3)
Age, yrs, (mean ± SD)	39.4 ± 15	40.3 ±14.4	47.0 ± 11.7***	41.1 ± 13.4
Duration of SLE, yrs (mean ± SD)	1.3 ± 0.9	NA	7.6 ± 7.0***	7.8 ± 6.8***
Race				
African American, n (%)	145 (63.3)	74 (26.7***)	51 (100.0)	58 (100.0)
With nephritis, n (%)	35 (24.1)	NA	29 (56.9***)	23 (39.7*)
Caucasian, n (%)	84 (36.7)	203 (73.3***)	0 (0.0)	0 (0.0)
With nephritis, n (%)	7 (8.3**)	NA	NA	NA

NA: not applicable.

* $p < 0.05$ compared to African American CLU cases,

** $p < 0.01$ compared to African American CLU cases,

*** $p < 0.0001$ compared to African American CLU cases (chi-square test, Fisher's exact test, or t-test, as appropriate).

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Table 2

Distribution of MPO genotypes by clinical and demographic subgroups within the 3 cohorts.

Clinical/Demographic Subgroup	GG, n (%)	GA, n (%)	AA, n (%)	A Allele Present, n (%)	A Alleles, %
CLU Cohort					
All SLE cases, n = 229	119 (52.0)	96 (41.9)	14 (6.1)	110 (48.0)	27.1
All controls, n = 277	167 (60.3)	101 (36.5)	9 (3.3)	110 (39.7)	21.5
Caucasian SLE cases, n = 84	46 (54.8)	36 (42.9)	2 (2.4)	38 (45.2)	23.8
With LN, n = 7	4 (57.1)	2 (28.6)	1 (14.3)	3 (42.9)	28.6
Without LN, n = 77	42 (54.6)	34 (44.2)	1 (1.3)	35 (45.5)	23.3
Caucasian controls, n = 203	130 (64.0)	69 (34.0)	4 (2.0)	73 (36.0)	19.0
AA SLE cases, n = 145	73 (50.3)	60 (41.4)	12 (8.3)	72 (49.7)	29.0
With LN, n = 35	12 (34.3)	20 (57.1)	3 (8.6)	23 (65.7)	37.1
Without LN, n = 110	61 (55.5)	40 (36.4)	9 (8.2)	49 (44.6)	26.4
AA controls, n = 74	37 (50.0)	32 (43.2)	5 (6.8)	37 (50.0)	29.2
Lupus Multiplex Registry and Repository					
AA SLE cases, n = 51	23 (45.1)	23 (45.1)	5 (9.8)	28 (54.9)	32.3
With LN, n = 29	9 (31.0)	15 (51.7)	5 (17.2)	20 (69,0)	43.1
Without LN, n = 22	14 (63.6)	8 (36.4)	0 (0.0)	8 (36.4)	18.2
Sea Island Lupus Cohort					
AA SLE cases, n = 58	22 (37.9)	22 (37.9)	14 (24.1)	36 (62.1)	43.1
With LN, n = 23	9 (39.1)	6 (26.1)	8 (34.5)	14 (60.9)	47.8
Without LN, n = 35	13 (37.1)	16 (45.7)	6 (17.1)	22 (62.9)	40.0
All cohorts					
AA cases with LN, n = 87	30 (34.5)	41 (47.1)	16 (18.4)	57 (65.5)	42.0
AA cases without LN, n = 167	88 (52.7)	64 (38.3)	15 (9.0)	79 (47.3)	28.1

AA: African American