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Genetic Risk Factors for Thrombosis in Systemic Lupus Erythematosus

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Abstract

Objectives—Thrombosis is a serious complication of systemic lupus erythematosus (SLE). We investigated whether genetic variants implicated in thrombosis pathways are associated with thrombosis among two ethnically diverse SLE cohorts.

Methods—Our discovery cohort consisted of 1698 SLE patients enrolled in the UCSF Lupus Genetics Project and our replication cohort included 1361 SLE patients enrolled in the PROFILE cohort. Patients fulfilled American College of Rheumatology SLE criteria and data relevant to thrombosis were available. Thirty-three single nucleotide polymorphisms (SNPs) previously shown to be associated with risk of deep venous thrombosis in the general population or implicated in thrombosis pathways were genotyped and tested for association with thrombosis in bivariate allelic analyses. SNPs with $p<0.1$ in the bivariate analyses were further tested in multivariable logistic regression models adjusted for age, sex, disease duration, anti-phospholipid antibody status, smoking, nephritis, and medications.

Results—In the discovery cohort, 23% of SLE patients experienced a thrombotic event. SNPs in the following genes demonstrated association with thrombosis risk overall in the discovery or replication cohorts and were assessed using meta-analytic methods: factor V Leiden (*FVL*) rs6025

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(OR 1.85, p 0.02) and methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 (OR 0.75, p 0.04) in European Americans and fibrinogen gamma (*FGG*) rs2066865 (OR 1.91, p 0.01) in Hispanic Americans. SNPs associated with venous thrombosis risk included: *MTHFR* rs1801131 (OR 1.51, p=0.01), *MTHFR* rs1801133 (OR 0.70, p=0.04), *FVL* rs6025 (OR 2.69, p=0.002) and *FGG* rs2066865 (OR 1.49, p=0.02) in European Americans. SNPs associated with arterial thrombosis risk included *FGG* rs2066865 (OR 2.19, p=0.003) in Hispanics.

Conclusion—Our results implicate specific genetic risk factors for thrombosis in patients with SLE and suggest that genetic risk for thrombosis differs across ethnic groups.

Keywords

systemic lupus erythematosus; thrombosis; polymorphism

INTRODUCTION

Thrombosis is a serious complication of systemic lupus erythematosus (SLE). Because SLE patients experience thrombotic events more frequently and at younger ages than the general population (1), morbidity from thrombosis is especially significant. For example, women with SLE aged 18–44 years are hospitalized with myocardial infarction or stroke almost 9 times more often than the general population (2). In a 10-year prospective study, thrombosis was as common a cause of death as infections and high disease activity (1). In a large Mexican lupus cohort, presence of the antiphospholipid syndrome conferred decreased survival (3). Furthermore, treatment with lifelong anticoagulation in this young population carries significant drawbacks, from frequent laboratory monitoring to severe bleeding complications. Better predictors of thrombosis are needed so that we can tailor treatment and prevent this potentially fatal disease complication.

Established risk factors for thrombosis in SLE include the presence of antiphospholipid antibodies (aPL) (4), smoking (5), longer disease duration, older age at SLE diagnosis (2) and disease activity (6). These known risk factors, however, do not completely explain the thrombosis burden in SLE. For example, among the 30–40% of SLE patients who produce antiphospholipid antibodies, only 10% experience a thrombotic event (7). Furthermore, 40% of SLE patients with thrombosis are aPL negative (8). Prior work by Chang and colleagues suggests that thrombosis risk is highest in the first year after SLE diagnosis (9), adding a sense of urgency to predicting this SLE-related clinical manifestation.

Most known genetic risk factors for thrombosis in the general population, such as the Factor V Leiden (*FVL)* and Prothrombin *G20210A* polymorphisms, are found predominantly in European Americans. However, striking ethnic differences in thrombosis exist in the general population and in SLE, the genetic underpinnings of which are virtually unexplored. For example, in the general population, Asian-Americans have a 3–5 fold lower incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE) than European Americans (10). African Americans have the highest rate of venous thromboembolism (11). Mok and colleagues demonstrated in a group of Chinese, African American and European American SLE patients that clinical factors alone could not explain the ethnic differences in incidence of thrombotic events (2). Genetic studies of thrombosis in the general population suggest that these risk factors might also help explain some of the variation in thrombosis outcomes among SLE patients of different ethnic backgrounds (12).

In this study, we investigated single nucleotide polymorphisms (SNPs) that have been previously associated with thrombosis in the general European American population (13) or have been implicated in thrombosis or coagulation pathways to determine whether they are associated with thrombosis in two multiethnic cohorts of SLE patients. We hypothesize that

these variants may increase risk of thrombosis in SLE in several potential ways. First, these SNPs may be associated with SLE itself. Alternatively, these SNPs may have the same prevalence in SLE but may be of increased importance in SLE because other risk factors for thrombosis are prevalent in SLE (e.g., aPL) and can provide the "second hit" required for a thrombotic event. Finally, these SNPs may be more common in non-European American ethnic groups, which are relatively overrepresented among individuals affected with SLE.

MATERIALS AND METHODS

Subjects

Discovery cohort—Because these SNPs have not been systematically examined for a role in thrombosis in the setting of SLE, we used a discovery/replication cohort design. Patients (n = 1698) in our multiethnic SLE discovery cohort were derived from the UCSF Lupus Genetics Project (14). The protocol was approved by the Institutional Review Board at the University of California, San Francisco (California, USA). Patients fulfilled ACR criteria for SLE (15), completed an extensive questionnaire, gave permission for medical record review, and provided a DNA sample. Individuals were recruited from diverse sources that included tertiary care and community hospitals and clinics as well as lupus support groups in northern California and nationwide.

Baseline questionnaire data included demographic, clinical, and behavioral factors. Thrombotic events were documented on the questionnaire and were confirmed by medical record review (where other thromboses not reported on the questionnaire were also confirmed). Thromboses considered included DVT, pulmonary embolism (PE), myocardial infarction (MI), cerebral vascular accident (CVA), recurrent miscarriages (at least 3 in the first trimester or one in the 2nd or 3rd trimester), and retinal vein thrombosis. Characteristics of the discovery cohort patients are shown in Table 1.

The main outcome variable was a history of at least one thrombotic event. Because certain genetic risk factors appear to be important in venous or arterial thrombosis, subgroup analyses were performed to evaluate these outcomes separately. Explanatory variables investigated for association with thrombosis risk included age at diagnosis, and SLE disease duration. Other explanatory variables available for a majority of patients included smoking (ever vs. never exposure), immunomodulating medications (including cyclophosphamide, azathioprine, methotrexate, and mycophenalate mofetil, ever vs. never use), nephritis, and the presence of anti-phospholipid (aPL) antibodies (lupus anticoagulant (LAC) measured by Russell Viper Venom Time (RVVT) (including confirmatory studies) and anticardiolipin (aCL) IgG and IgM). aPL positivity was defined as at least one laboratory test documented to be positive.

Replication Cohort—Our replication cohort consisted of 1361 SLE patients from the PROFILE cohort (16). PROFILE is a multi-institutional cohort recruited from Northwestern University, Johns Hopkins University, the University of Alabama at Birmingham, the University of Texas Health Science Center at Houston, and the University of Puerto Rico. Patients meet ACR criteria, are at least 16 years of age, and have a disease duration of 10 years at cohort entry. Phenotype data from these SLE patients were obtained as part of this cohort's protocol and included age, sex, ethnicity, smoking history, nephritis, aPL, medication use, and thrombosis outcomes of DVT, CVA, and MI (Table 1).

SNP Selection and Genotyping

Primary predictors included SNPs associated with DVT in a large non-SLE case-control study (13). Established and suggested genetic risk factors for thrombosis in the general

population and in SLE in the literature (e.g. MBL (17)) were also investigated. Table 2 lists all 33 SNPs.

For rs6048 and rs2289252, genotyping was done by allele-specific real-time PCR using assays designed and validated at Celera. Genotyping accuracy on this platform has been found to be greater than 99% (18). For other SNPs, genotyping was performed using the Luminex multiplex technology in which genotypes were determined automatically by passing the raw Luminex L-100 signal data through an unsupervised classification algorithm. Approximately 96 to 98% of all genotypes were autocalled. A final manual review of the data was performed to assess each assay's technical performance in order to rescue any aberrant genotype autocalls.

Among the discovery cohort, nine SLE patients were dropped from analysis due to failure to amplify and 11 patients were dropped because their self-reported sex did not match sex typing. We had 299 trios available among cases in the discovery cohort that were used for quality control. Forty genotypes were set to missing after PedCheck for Mendelian errors was performed in these trios. Missingness per SNP and per subject was low (1–2.32% and <0.03%, respectively). No additional subjects were dropped based on these criteria among the PROFILE cohort patients. Deviations from Hardy-Weinberg Equilibrium were assessed using an exact test and no deviations were observed.

Ancestry informative markers (AIMs)

Ancestry informative markers (AIMs) were available for a majority of the discovery cohort patients (n=1595). These were used to identify population outliers for sensitivity analysis, using STRUCTURE (K=5 populations) ancestry estimates. Subjects were removed if they had >15% South Asian (the 5th population); were self-reported European American, African American, or Asian but were outliers by the box test (beyond 1.5*Inter-Quartile Range) of percent European, South African, or East Asian, respectively; or were Hispanic patients with box test failure for Amerindian plus European, <15% Amerindian or >15% South African. We performed subgroup analyses on the remaining patients to see if results differed after removal of outliers and adjusting for ancestry.

Statistical analysis

SNPs were coded according to the presence or absence of the minor allele. SNPs that were significantly associated with thrombosis in bivariate allelic analyses performed for each major ethnic subgroup ($p<0.10$) were tested in multivariable logistic regression models to adjust for age, sex, disease duration, aPL, smoking history, nephritis, and medication use. Each SNP was the primary predictor. Because the B, C, and D MBL variant alleles each have large effects on MBL concentrations, they were grouped into one O allele for analysis (A being wildtype) as is standard in the literature and genotypes were analyzed as A/A, A/O or O/O (19). Other SNPs did not demonstrate major linkage disequilibrium with the exception of *rs13146272* which is in LD with the F11 SNPs. Meta-analytic techniques using random effects (using the "meta" STATA function) were used to compare odds ratios (OR) within ethnic groups for SNPs found to be significant in logistic regression analyses in either the discovery or replication cohorts. We chose a more conservative random-effects meta-analysis approach (versus pooling) to account for differences in the cohorts. Our primary outcome was all thrombotic events but we also considered venous and arterial thrombosis separately in sensitivity analyses because data suggests that certain genes or variants contribute specifically to venous or arterial thrombosis. We performed a sensitivity analysis in which we excluded subjects for whom miscarriage was their only thrombosis because basic science evidence suggests mechanisms for thrombosis may differ in this subgroup (20).

Multiple testing is an important issue in our analyses, since we start with 33 loci in four ethnicities and three outcomes (venous thrombosis, arterial thrombosis, any thrombosis). Because our outcomes are not independent and associations may or may not be ethnicity-specific, we believe that the primary concern for multiple testing is the 33 loci. Therefore results of the meta-analyses were adjusted for multiple testing at 33 loci using the false discovery rate (FDR) control procedures (21).

Statistical analyses were performed using the STATA SE software, version 11.0 (StataCorp, College Station, Texas, USA), HAPLOVIEW (22), PedCheck (23), PLINK (24), STRUCTURE (http://pritch.bsd.uchicago.edu/structure.html) (25) and R (http://www.R-project.org) (26).

RESULTS

Characteristics of the 1698 SLE patients in the discovery cohort are shown in Table 1. Ninety two percent of subjects were female and 60% were European American (with 15% Hispanic, 13% Asian-American and 12% African-American ancestry). The mean age at SLE diagnosis was 33 years and the mean disease duration was nine years. Approximately 23% of subjects experienced at least one thrombosis. Thirty-five percent of subjects were aPL positive. Characteristics of the 1361 SLE patients in the replication cohort (also shown in Table 1) were similar to the discovery cohort in terms of age at disease onset and proportion of females, but there were fewer European Americans and Asian-Americans and more African-Americans, consistent with the different geographic recruitment sites for this cohort. In addition, 23% of subjects in the Discovery Cohort experienced at least one thrombosis while only 12% of subjects in the Replication Cohort experienced a thrombotic event. This difference in numbers of thrombotic events between the cohorts likely reflects differences in the recording of thrombotic events, with fewer types of events recorded in the Replication Cohort since this cohort was not specifically designed to study the outcome of thrombosis in lupus.

Results of multivariable analyses for thrombosis outcomes (venous, arterial or any thrombosis) for the discovery and replication cohorts are shown in meta-analyzed form in Table 3. Twenty-three SNP-ethnicity pairs passed bivariate and logistic regression screening ($p<0.10$) and were included in the meta-analysis. The p values for heterogeneity (p_{het}) were nonsignificant, supporting combined analysis using meta-analytic techniques. In a sensitivity analysis, we repeated the analyses excluding the 218 subjects who had miscarriages as their only thrombosis. Results were similar except for one additional association found for arterial thrombosis in Hispanics: *MBL* (OR 2.70 (1.23–5.94) p=0.013).

Meta-analysis results for the main outcome of thrombosis revealed significant association ($p<0.05$) with the following SNPs across cohorts: *FVL* rs6025 (OR 1.85, p=0.02), *MTHFR* rs1801133 (OR 0.75, p=0.04) for European Americans and, *FGG* rs2066865 (OR 1.91, p=0.01) for Hispanics. For venous thrombosis, results of meta-analysis revealed the following statistically significant associations across cohorts: *MTHFR* rs1801131 (OR 1.51, p=0.01), *MTHFR* rs1801133 (OR 0.70, p=0.04), *FVL* rs6025 (OR 2.69, p=0.002) and *FGG* rs2066865 (OR 1.49, p=0.02) in European Americans. For arterial thrombosis, results of meta-analysis revealed the following statistically significant associations across cohorts: *FGG* rs2066865 (OR 2.19, 0.003) in Hispanics.

To evaluate whether confounding by ethnicity influenced our results, we performed this same analysis among a large subgroup of the discovery cohort (n=1595) for whom ancestry informative marker (AIM) data were available. In a bivariate analysis, we first evaluated whether ancestry was associated with our thrombosis outcomes. When associated, we also

adjusted for percent ancestry in our logistic analyses. Meta-analysis results across cohorts were similar to our main results.

DISCUSSION

We found that genetic variants of *FGG* rs2066865, *MTHFR* (*rs1801133* and *rs1801131*), and *FVL rs6025* are associated with risk of thrombosis among European American SLE patients and *FGG also* appears to be a risk factor for thrombosis in Hispanic SLE patients. Interestingly, the effect sizes for these associations are similar to those found in a recent GWAS of venous thrombosis in the general European American population. Furthermore, when miscarriages are removed from analysis, association with one additional SNP (MBL OR 2.70, 95% CI: 1.23–5.93, p=0.013) was identified for arterial thrombosis among Hispanics. The fact that most initial results remained significant suggests that the genetic predisposition for obstetric and non-obstetric thrombosis may be similar.

In the general population, several inherited genetic polymorphisms have been shown to independently confer risk of DVT. For example, the relative risk for DVT among individuals heterozygous for *FVL* was 6.6 compared to 80 for homozygotes (27). We recently performed an individual patient data meta-analysis and found that the presence of the *FVL* polymorphism is associated with an almost three-fold increased thrombosis risk compared to SLE subjects without this polymorphism, even when adjusting for other known risk factors (28). This lower effect size compared to the FVL studies in the general population suggests that for some polymorphisms, other risk factors for thrombosis in SLE may be equally or more important to thrombosis risk than in the general population. We confirmed this association with FVL rs6025 and venous thrombosis in SLE (OR 2.58, p=0.002) in European American SLE patients in this study.

Certain SNPs appear to be more important in certain ethnic subgroups, e.g., *FGG rs2066865* in SLE patients of Hispanic ethnicity. Although established genetic risk factors for thrombosis are described mainly for European Americans to date, other ethnic groups tend to have worse outcomes (African Americans, Hispanics) (29) and genetic risk factors for thrombosis may contribute to this difference beyond traditional explanations (such as socio-economic status).

Other polymorphisms implicated as risk factors for SLE development, severity, and infections such as mannose binding lectin (MBL) (19) have also been implicated in thrombosis risk in SLE. One study found an increased risk of arterial thrombosis among SLE patients homozygous for the MBL variant (30). Another found that MBL variant alleles were only associated with cerebrovascular events in European Americans (17). Yet another found no association between MBL variant alleles and arterial thromboses (31). Interestingly, Seelen et. al. found that aCL autoantibodies occurred more frequently in patients with MBL variant alleles (32). When we removed miscarriages from consideration in a subgroup analysis, we found that MBL variant alleles were associated with arterial thrombosis among Hispanics (OR 2.70 (1.23–5.93, p=0.013). Thus the relationship between MBL alleles and thrombosis in SLE is incompletely understood but may vary by ethnicity. Further study of these variants in non-European ethnic groups is warranted given the relatively smaller numbers of these individuals in the current study.

Polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene result in decreased ability to eliminate plasma homocysteine (33, 34). Resulting elevated homocysteine levels may predispose to thrombosis although this relationship is not well-established (35). Prior research in SLE has been inconclusive (36, 37). The results of our

study suggest that these polymorphisms may be important in thrombosis risk in SLE, at least among European American SLE patients.

For stablilization of thrombi to occur, thrombin-induced conversion of fibrinogen to fibrin must take place. Furthermore, elevated plasma fibrinogen levels are associated with both increased platelet aggregation and plasma viscosity. A SNP (rs2066865) in the fibrinogen gamma gene (FGG) has been associated with DVT risk in an Austrian study (38). We found that this SNP may be important in thrombosis risk in Hispanics.

The *F9 Malmö* rs6048 polymorphism has been associated with venous thrombosis in non-SLE European Americans (39). We found that *F9* rs6049 was an important risk factor for thrombosis risk in Hispanics in our Discovery cohort but we did not have enough observations to confirm these results in our replication cohort. Replication of these findings in larger, independent Hispanic patient populations is therefore warranted.

Although we had limited power to investigate less common polymorphisms in non-European American ethnic groups, this study is the largest and most ethnically diverse investigation of genetic risk factors for thrombosis to date in SLE and thus provides valuable data for future investigations of this important outcome. This is also the only such study to date to incorporate so many pertinent covariates into the analysis of genetic risk factors. Because these cohorts were not specifically designed to study the outcome of thrombosis, the replication cohort may have underestimated thrombotic events (therefore misclassifying SLE patients who have actually had a thrombotic event) because only MI, DVT, and CVA were captured in this cohort. However, this would presumably decrease our ability to identify significant genetic associations and thus represents a conservative bias. Finally, we were unable to adjust for important risk factors for thrombosis such as lipid levels, obesity, BMI, hypertension and diabetes. Given the average age of our patients (33 years), some of these risk factors (e.g., diabetes) may not have been prevalent but others (e.g., hypertension from renal disease, early hyperlipidemia) may be important.

Because we did not have AIM data on all patients, population stratification may have influenced our results, however, our subgroup analyses in which AIM data were incorporated suggests that population stratification was not a major confounding factor in this study. Finally, although we limited this study to polymorphisms that have been previously associated with thrombosis or coagulation pathways, the number of comparisons performed raise the risk of false positive association results. For this reason, we used a discovery/replication cohort study design and employed FDR in a sensitivity analysis. Although only two results remained significant after multiple testing correction, the consistency of ORs and FDR-adjusted p-values <0.1 in Table 3 suggests that there are additional true associations between these loci and thrombosis outcomes that may be confirmed in other populations.

In the future, genetic information may help predict which SLE patients are at greatest risk for thrombotic events. Neville et al. have demonstrated that among aPL positive subjects who have not experienced a thrombosis, there is a significant increased risk of a thrombotic event (40). Therefore, identifying risk factors for this subset of patients may be useful in risk-stratifying patients for treatment with anticoagulation in the future, especially if new anticoagulants can be developed that have safer risk profiles and are easier to monitor than warfarin. Examining genetic risk factors for thrombosis in SLE may not only help to understand pathogenesis but also inform prediction of this SLE complication.

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Table 1

Patient Characteristics

Characteristics	Discovery Cohort, n=1698 n (%)	Replication Cohort n=1361 n (%)
Female	1554 (92)	1248 (92)
Ethnicity		
European Americans	1015 (60)	621 (46)
Hispanic	247 (15)	217 (16)
Asian/Pacific Islander	230 (13)	33 (2)
African American	206 (12)	490 (36)
Age at SLE diagnosis mean (standard deviation)	33 (13.4)	34 (13)
Duration of SLE, mean, (range in years)	9 (8.3, 1–41)	13 (6)
Ever smoker	666 (39)	191 (14)
Nephritis	562 (33)	504 (37)
Immunomodulator therapy	957 (56)	574 (45)
Prednisone treatment	1512 (89)	952 (75)
Hydroxychloroquine	1397 (82)	991 (78)
At least one thrombosis		
European Americans	236 (23)	72 (12)
Hispanic	61 (25)	13 (6)
Asian/Pacific Islander	40 (17)	2 (6)
African American	45 (22)	53 (11)
Total	382 (22)	140 (10)
Number of thromboses:		
0	1316 (78)	1221 (90)
1	272 (16)	127 (9)
2	89 (5)	12 (<1)
3	16 (1)	1 (<1)
4	4 (<1)	0
5	1 (<1)	0
Thrombosis types:		
Deep venous thrombosis	119	31
Pulmonary embolism	51	--~
Cerebral Vascular accident	90	91
Myocardial infarction	42	32
Retinal vein	14	--~
Miscarriage in 1st trimester (3 consecutive)	7	--~
Miscarriage late (≥ 1 in 2nd or 3rd trimester)	137	--~
Other thromboses	59	--~
Total # thromboses	519	154
aCL* *or* LAC^ *or* B2GP1~ positive	589 (35)	153 (11)

*anticardiolipin IgG or IgM,

^ lupus anticoagulant (RVVT),

~ Beta2 Glycoprotein 1 IgG or IgM,

~ unavailable for this project

Table 2

SNPs investigated in this study

#	RS Number	gene	Type of polymorphism	Biologic Pathway
1	rs1799963	F2	UTR3	Coagulation cascade/natural anticoagulation
2	rs6025	F5 Leiden	Silent mutation	
3	rs1800595	F5 (R2 allele)	Missense mutation	
4	rs4524	F5	Missense mutation	
5	rs6049	F9	Donor splice site	
6	rs6048	F9 Malmö	Missense mutation	
7	rs2036914	F11	Intron	
8	rs2289252	F11	Intron	
9	rs3756008	F11	Intergenic	
10	rs13146272*	CYP4V2	Missense mutation	
11	rs2227589	SERPINC1	Intron	
12	rs2066865	FGG	Intergenic	
13	rs1800450	MBL2	Missense mutation	Innate immunity/complement
14	rs1800451	MBL2	Missense mutation	
15	rs5030737	MBL2	Missense mutation	
16	rs1838065	MBL2	Intron	
17	rs7096206	MBL2	Intergenic	
18	rs9332245	CYP2C9	Intergenic	Warfarin Metabolism
19	rs1799853	CYP2C9	Missense mutation	
20	rs9923231	VKORC1	Intergenic	
21	rs9934438	VKORC1	Intron	
22	rs1801690	APOH	Missense mutation	Glycoproteins
23	rs1613662	GP6/RDH13	Missense mutation	
24	rs1801131	MTHFR	Missense mutation	Homocysteine metabolism
25	rs1801133	MTHFR	Missense mutation	
26	rs20455	KIF6	Missense mutation	Other
27	rs2001436	NAT8B	Intergenic	
28	rs1523127	NR1|2	UTR5	
29	rs2234628	XYLB	Intron	
30	rs1417121	AKT3	Intron	
31	rs2266911	ODZ1	Intron	
32	rs670659	RGS7	Intron	
33	rs2585008	CASP8AP2	Intron	

*This SNP is in linkage disequilibrium with the F11 SNPs

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Table 3

Meta-analysis[†] results for genetic variants associated with thrombosis in multivariable[‡] analyses in either the discovery or replication cohorts[₣]

SNP	Gene	MAF[++]	Ethnic Group	Discovery cohort OR[^] (CI[~]) p[**]	Replication cohort OR (CI) p	OR MH[+] (p)	FDR[’] p value
All thrombosis							
rs6025	*FV Leiden*	0.030	European American	**2.02 (1.16–3.51) 0.013**	1.10 (0.29–4.18) 0.893	**1.85 (0.019)**	0.11
rs2234628	*XYLB*	0.147	Hispanic	**0.48 (0.23–0.99) 0.047**	2.22 (0.64–7.69) 0.206	0.95 (0.94)	1
rs9923231	*VKORC1*	0.119	African American	**2.44 (1.19–5.01) 0.015**	1.29 (0.77–2.87) 0.236	1.74 (0.080)	0.26
rs6049	*F9*	0.003	European American	Too few observations	**17.14 (2.10–140.02) 0.008**		
rs2066865	*FGG*	0.229	Hispanic	1.69 (0.96–2.98) 0.071	**2.79 (1.03–7.56) 0.043**	**1.91 (0.010)**	0.083
rs2001436	*NAT8B*	0.358	African American	1.02 (0.59–1.77) 0.080	**0.60 (0.37–0.96) 0.034**	0.77 (0.31)	0.84
rs1801131	*MTHFR*	0.316	European American	1.17 (0.92–1.48) 0.190	**1.65 (1.03–2.65) 0.038**	1.30 (0.096)	0.29
rs1801133	*MTHFR*	0.338	European American	0.81 (0.64–1.02) 0.076	0.58 (0.34–0.97) 0.04	**0.75 (0.042)**	0.15
Venous thrombosis							
rs1801131	*MTHFR*	0.316	European American	**1.53 (1.10–2.13) 0.013**	1.42 (0.62–3.28) 0.406	**1.52 (0.008)**	0.083
rs1801133	*MTHFR*	0.338	European American	**0.68 (0.47–0.97) 0.035**	0.86 (0.35–2.14) 0.75	**0.70 (0.040)**	0.15
rs6025	*FV Leiden*	0.030	European American	**2.71 (1.37–5.34) 0.004**	2.52 (0.38–16.68) 0.337	**2.69 (0.002)**	**0.050**
rs6049	*F9*	0.001	Hispanic	**12.78 (1.93–84.41) 0.008**	Not enough observations	-	-
rs2066865	*FGG*	0.234	European American	**1.55 (1.08–2.24) 0.018**	1.10 (0.40–3.02) 0.85	**1.49 (0.023)**	0.11
rs4524	*F5*	0.365	Hispanic	**0.38 (0.16–0.86) 0.020**	Not enough observations		
rs6048	*F9 Malmo*	0.282	European American	0.86 (0.60–1.25) 0.43	**0.07 (0.01–0.57) 0.013**	0.30 (0.33)	0.84
rs2289252	*F11*	0.404	European American	0.85 (0.61–1.19) 0.335	**3.10 (1.33–7.24) 0.009**	1.53 (0.51)	1
rs2036914	*F11*	0.470	European American	1.03 (0.75–1.43) 0.838	**0.30 (0.12–0.73) 0.008**	0.60 (0.40)	0.95
rs3756008	*F11*	0.400	European Americans	0.87 (0.62–1.22) 0.417	**3.24 (1.39–7.55) 0.006**	1.58 (0.48)	1
Arterial thrombosis							
rs9934438	*VKORC1*	0.183	Asian Americans	**0.36 (0.18–0.75) 0.006**	Not enough observations	-	-
rs9923231	*VKORC1*	0.181	Asian Americans	**0.36 (0.18–0.75) 0.006**	Not enough observations	-	-
rs2266911	*ODZ1*	0.046	European Americans	**0.67 (0.47–0.96) 0.029**	1.30 (0.70–2.43) 0.406	0.89 (0.71)	1
rs20455	*KIF6*	0.210	African Americans	1.49 (0.65–3.46) 0.345	**0.56 (0.31–0.99) 0.047**	0.87 (0.78)	1
rs2066865	*FGG*	0.229	Hispanic	1.93 (1.04–3.57) 0.037	**3.08 (1.13–8.39) 0.028**	**2.19 (0.003)**	**0.050**

SNP	Gene	MAF++	Ethnic Group	Discovery cohort OR^ (CI~) p**	Replication cohort OR (CI) p	OR MH+ (p)	FDR' p value
rs2585008	*CASP8AP2*	0.388	African Americans	0.69 (0.36–1.32) 0.258	**0.58 (0.34–0.99) 0.044**	0.62 (0.024)	0.11

† random effects,

‡ adjusted for age, sex, disease duration, aPL (antiphospholipd antibody) status, nephritis, smoking history, immunomodulating medication history,

++ minor allele frequency in all SLE patients,

^ Odds ratio,

~ 95% Confidence interval,

** p value,

+ MH=Mantel Haanzel,

' False Discovery Rate,

Ŧ European American patients in the discovery cohort were also included in an individual patient data meta-analysis of the FVL polymorphism published in *Genes and Immunity (10: 495, 2009)*