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Factor V Leiden and Thrombosis in Patients with Systemic Lupus Erythematosus (SLE): A Meta-analysis

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Abstract

To perform a meta-analysis of the association between the factor V Leiden polymorphism (FVL) and thrombosis among patients with SLE and/or antiphospholipid antibody (aPL) positivity. Included studies recruited patients based on SLE or aPL positive status, confirmed subjects' SLE diagnosis as defined by the American College of Rheumatology, and documented thrombotic events. Excluded studies were non-English or considered only arterial thrombosis. Individual patient data, available from five studies, together with unpublished data from 1210 European-American SLE patients from the UCSF Lupus Genetics Collection genotyped for FVL, were further analyzed. Seventeen studies (n=2090 subjects) were included in the initial meta-analysis. Unadjusted odds ratios (OR) were calculated to assess association of FVL with thrombosis. The OR for association of thrombosis with FVL was 2.88 (95% C.I. 1.98-4.20). In the secondary analysis with our individual patient dataset (n=1447 European-derived individuals), SLE subjects with the FVL polymorphism still had more than two times the odds of thrombosis compared to subjects without this polymorphism, even when adjusting for covariates such as gender, age, and aPL status. SLE and/or aPL positive patients with the FVL variant have more than two times the odds of thrombosis compared to those without this polymorphism.

Keywords

Systemic lupus erythematosus; factor V Leiden polymorphism; thrombosis; risk factors; antiphospholipid antibodies

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with diverse clinical manifestations. Some SLE patients develop a malar rash, arthralgias, and

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characteristic autoantibodies while others experience life-threatening manifestations such as nephritis or thrombosis. A thrombotic event can manifest as a cerebral vascular accident (CVA), deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), retinal vein thrombosis, or recurrent miscarriages. Because a thrombotic event can be devastating, and because treatment is life-long anticoagulation (which itself carries significant bleeding risks), identifying risk factors for thrombosis in SLE patients is crucial to preventing undesirable outcomes.

In a large European study, thrombosis was responsible for 27% of SLE mortality1 and significant morbidity. In another ten-year prospective study of SLE patients, thrombosis was the second most frequent cause of death.1 One established risk factor for thrombosis is production of anti-phospholipid antibodies (aPL). These antibodies are a heterogeneous group of immunoglobulins directed against epitopes that result from the interaction of phospholipids and proteins such as annexin V, prothrombin, cardiolipin and ß2glycoprotein. APL are associated with an increased risk of venous and arterial thrombosis but the mechanism of increased risk is not well understood.2 Thirty to forty percent of SLE patients produce these autoantibodies but only 10% of those patients experience a thrombotic event.3 This risk factor does not fully explain the increased thrombosis risk in SLE because 40% of SLE thrombosis cases are aPL negative. 4 Other established risk factors for thrombosis include smoking 5, longer disease duration, and older age at SLE diagnosis. 6

A polymorphism in a gene involved in the coagulation cascade - Factor V - may explain part of this increased thrombosis risk in SLE patients. Normally, a balance exists between the factors in the clotting cascade which lead to the formation of thrombin and the natural anticoagulants such as activated protein C which help maintain a balance between bleeding and clot formation. Once the clotting cascade is activated, Factor V is one in a series of factors whose sequential activation leads to the formation of a cross-linked fibrin clot. The Factor V Leiden (FVL) polymorphism (the risk variant) is a single point mutation resulting in a guanine to adenine substitution at nucleotide position 1691. The presence of this point mutation confers resistance to activated protein C, and thus shifts the balance towards thrombosis in the clotting cascade. All individuals with FVL share the same FV haplotype, suggesting a founder effect.7 FVL has a five to seven percent prevalence in Europeans and is especially common (up to 15%) in southern Sweden, Germany, and Cyprus.7

FVL is the most common inherited risk factor for venous thrombosis in the general population. The FVL variant is found in 20-60% of (non-SLE) patients with idiopathic DVT.8 The relative risk for subjects heterozygous for FVL and DVT occurrence was 8.1 in the Leiden Thrombophilia Study and 80 for subjects homozygous for the polymorphism.9 Many studies have examined the association of FVL with thrombosis in SLE, however, most have been underpowered. Because SLE patients have a higher incidence of thrombosis than the general population, even in the absence of aPL (the most established risk factor for thrombosis in this population), the effect of this polymorphism in SLE may be different than in the general population. Indeed, only 22% of subjects with aPL without SLE develop thrombosis, but 70% of patients with both aPL and SLE develop thrombosis 10, suggesting that different mechanisms and risk factors account for thrombosis in SLE patients.

To assess FVL as a risk factor for thrombosis in SLE patients and to quantify any increased risk, we undertook a meta-analysis of the published literature. We also performed an individual patient data meta-analysis using primary data contributed by individual authors where available, as well as unpublished data from the University of California, San Francisco (UCSF) Lupus Genetics collection11. This larger secondary analysis not only improved our power to detect an association between FVL and thrombosis in SLE patients - a limitation to drawing conclusions from the original studies - but also allowed us to control for important covariates such as age, gender, smoking, and aPL status. The analysis of individual patient level data also facilitated analysis of particular subgroups of thrombosis, such as venous thrombosis.

RESULTS

Study characteristics

Literature search results are shown in Figure 1. The initial search identified 374 articles. Three potentially relevant non-English publications were identified. An article written in Polish and one of the two Russian articles were excluded based on review of the English abstract. The second Russian article could not be found in English and was also excluded. Seventeen articles remained after inclusion and exclusion criteria were applied and were evaluated for the association of FVL with thrombosis in SLE patients. A total of 2090 SLE and/or aPL positive patients were included in this preliminary meta-analysis. Characteristics of included studies are shown in Table 1. Eight studies recruited subjects based on aPL status (many of whom had SLE), 6 studies recruited subjects based on SLE status (many of whom were aPL positive), and 3 studies recruited both aPL positive and SLE subjects. All studies were retrospective. Studies were performed in a wide variety of countries including the United States (3 studies)12-14, Canada (3 studies)10,15,16, the Netherlands (2 studies) 17,18, Italy (2 studies) 8,19, Hungary (2 studies) 20,21, and one study each from Sweden 22, England 23, Spain 24, Turkey 25, and Argentina 26. Five studies included small proportions of non-European subjects 10,12-14,16 (which we were able to exclude from the individual patient data meta-analysis).

Using a standardized form, we abstracted data on study design, study setting, sample size, enrollment criteria, number of SLE and/or aPL positive subjects, ethnicity, covariates considered, type of thromboses considered, number of subjects with lupus anticoagulant and/or anti-cardiolipin antibody, number of subjects with at least one thrombotic event, and number of subjects with multiple events. In order to calculate unadjusted odds ratios (OR) for the association between FVL and thrombosis, we also abstracted the number of patients with FVL (both with and without thrombotic events) and the number of patients who were FVL negative (both with and without thrombotic events).

Eight hundred twenty-one subjects (39%) had a thrombotic event, 1099 (53%) had SLE and 1245 (60%) were aPL positive. One hundred thirty-four (6.4%) were FVL (risk allele) positive. All but two studies8,13 clearly stated that they confirmed thrombotic events using medical records and x-ray reports. Types of thromboses assessed in these studies varied. Some studies considered broad categories of venous and arterial thromboses12,13,23. Most studies considered many different types of thromboses including DVT, PE, CVA, MI,

retinal vein thrombosis, recurrent miscarriages in the first trimester, and at least one miscarriage in the second or third trimester. Most patients who tested positive for FVL were heterozygous and only two studies included a patient homozygous for FVL.8,21 Most studies measured both anti-cardiolipin and lupus anticoagulants. Three recent studies also measured ß2glycoprotein. 10,16,21

Publication bias assessment

To determine if publication bias existed among our seventeen included studies, we first generated a funnel plot (Figure 2). This plot did not reveal substantial asymmetry (there were similar numbers of negative and positive results). We then performed Egger's regression asymmetry test, a statistical test to assess for publication bias. The results indicated no evidence for publication bias ($p = 0.46$).

Summary statistics

A Mantel-Haenszel test statistic was used to assess homogeneity. There was no evidence to reject the null hypothesis that the studies were homogeneous ($p = 0.72$) therefore, data were combined using the Mantel-Haenszel method (fixed effects model) to obtain a summary estimate and these results are displayed in a Forrest plot in Figure 3. ORs for association of FVL with thrombosis in individual studies range from 1.5 to 20 with one study obtaining an OR of 0.4 (Sasso et. al.), indicating an inverse association (although this was not a statistically significant finding). Most confidence intervals had wide ranges and included 1.0, and therefore were not statistically significant. The pooled OR for association of FVL with thrombosis was 2.88 (95% C.I. 1.98 - 4.20). ORs were also calculated separately for studies that recruited patients based on aPL positivity and studies that recruited patients based on an SLE diagnosis to determine whether results of these studies differed. The pooled OR for studies that recruited patients based on aPL status was 2.87 (95% C.I. 1.60-5.16) and for those that recruited subjects based on SLE status was 2.69 (95% C.I. 1.56-4.62). Because these ORs were similar, all studies were pooled in the final analysis.

Individual Patient Data Results

For our secondary meta-analysis, we queried all authors of the original manuscripts to request individual level patient data in order to calculate the association between FVL and thrombosis while also adjusting for relevant covariates such as age, gender, smoking status and aPL. This data also allowed for subgroup analysis, for example, analysis of subjects who specifically had a DVT. Seven of seventeen authors responded to our query and five contributed individual patient level data. In addition, we included 1210 SLE subjects from the UCSF Lupus Genetics Collection genotyped for FVL and with well-described covariates and thrombosis outcomes. Thus, a total of 2030 subjects were available for analysis in this dataset.

Among these subjects, the average age was 43 (S.D. 13.8), 1691 (83%) subjects were female, 1359 (67%) were of European-derived ancestry, 104 (5%) tested positive for the FVL polymorphism, 621 (31%) experienced a thrombotic event, 675 (33%) were ever-smokers, and 1046 (51%) had been treated with hydroxychloroquine. Eight hundred ten (40%) subjects were aCL (anti-cardiolipin) or LAC (lupus anticoagulant) positive. One

hundred seventy-two (8.5%) subjects had a DVT, 56 (2.8%) had a PE, 106 (5.2%) had a CVA, 52 had an (2.6%) MI, and 6 (0.3%) had a retinal vein thrombosis. Four hundred thirty-one (21%) had more than one thrombotic event.

Associations between FVL and thrombosis were first calculated separately for SLE patients and for aPL (anti-phospholipid antibody) positive patients. Calculations were restricted to European-derived subjects (n=1447) since FVL is present exclusively in European-derived populations. Bivariate analyses were performed in which each predictor was tested for association with thrombosis (Table 4). Bivariate analysis in European-derived subjects with SLE demonstrated statistically significant associations between thrombosis and the following predictors: FVL (OR 1.81, 95% C.I. 1.05-3.06), aPL positivity (LAC or aPL) (OR 2.84, 95% C.I. 2.11-3.82), and age (OR 1.19 per 10 years, 95% C.I. 1.06 - 1.32) but not with gender or smoking status. Bivariate analyses in European-derived subjects who were aPL positive demonstrated statistically significant associations between thrombosis and FVL (OR 2.34, 95% C.I. 1.13-5.02), gender (OR 0.34 for female gender, 95% C.I. 0.21 - 0.57), and smoking (OR 1.62, 95% C.I. 1.08-2.42) but not with age or SLE status.

In a logistic regression model examining European-derived patients (Table 2), age (OR 1.20 per 10 years, 95% C.I. 1.09 - 1.33), gender (OR 0.44 for female gender, 95% C.I. 0.30 - 0.63), FVL (OR 1.91, 95% C.I. 1.16 - 3.16), smoking status (OR 1.38, 95% C.I. 1.05 - 1.82) and aPL positive status (OR 4.54, 95% C.I. 3.45 - 5.97) were significantly associated with thrombosis. This model evaluated the association of our primary predictor (FVL) with thrombosis while adjusting for the other covariates. When this logistic regression analysis was restricted to SLE patients, similar results were obtained with age (OR 1.29, 95% C.I. 1.14 - 1.46), and aPL positivity (OR 4.05, 95% C.I. 2.92 - 5.61) significantly associated with thrombosis and borderline significant results supporting an increased thrombosis risk associated with FVL (OR 1.76, 95% C.I. 0.99 - 3.12). Therefore, even when adjusting for other covariates, FVL was still associated with thrombosis, confirming the results of the original meta-analysis with a slightly lower OR for the association of FVL with thrombosis. Interaction terms were also evaluated between FVL and smoking and FVL and aPL. No evidence of interaction was found.

Sensitivity analyses were performed in order to determine whether the results would be substantially different when certain model parameters were changed. If the results differ substantially when a small change is made in a parameter then the results are sensitive to that particular parameter. For example, several individual studies considered both venous and arterial thromboses in their outcome definition, however, FVL has been shown to be a risk factor specifically for venous thromboses. To address this point, we first did a sensitivity analysis on 936 European-derived SLE patients for whom venous thrombosis information was available (Table 3). FVL (OR 3.19, 95% C.I. 1.60-6.35) and aPL (OR 4.49, 95% C.I. 2.71-7.43) were risk factors for venous thrombosis while female gender was protective (OR 0.46, 95% C.I. 0.23-0.91).

We also performed a sensitivity analysis on a group of 942 European-derived SLE subjects for whom DVT information was specifically available (a subset of the subjects with venous thrombosis). Results were similar with gender (OR 0.47 for female, 95% C.I. 0.23 - 0.96),

FVL (OR 2.33, 95% C.I. 1.09 - 4.92), and aPL (OR 4.19, 95% C.I. 2.54 - 6.91) being statistically significant risk factors. Of note, the OR for FVL was higher when these venous outcomes were considered individually.

Subgroup analyses were also performed in European SLE patients for whom the explanatory variable aPL was considered separately as LAC and aCL (IgG or IgM). In these smaller analyses (n=329), FVL (OR 4.84, 95% C.I. 1.30-17.96) and LAC (OR 8.84, 95% C.I. 3.35-23.29) were statistically significant risk factors for thrombosis.

To assess representativeness of the included datasets, we compared included studies to those which did not contribute individual patient-level data. Included studies spanned the publication dates of all studies so results were not biased toward recent publications. Included studies were all from English-speaking nations including the USA, England, or Canada. While most studies included SLE subjects, five of the six studies included in the individual patient data meta-analysis recruited based on aPL positive status, which may have biased towards subjects likely to have thrombosis. The addition of 1210 SLE subjects from the UCSF Lupus Genetics Collection recruited based on SLE status, however, should help to reduce this bias.

DISCUSSION

Patients with SLE or aPL and the FVL polymorphism have more than two times the odds of thrombosis compared to patients without this polymorphism. Considered individually, most studies included in our meta-analysis did not reveal a statistically significant association with thrombosis, (shown in Table 1 and in Forrest plot), perhaps due to small sample sizes and hence limited statistical power of these individual studies. For example, to detect an association of FVL with thrombosis given the prevalence of FVL and the frequency of thrombosis in the SLE population, a sample size of at least 900 subjects would be required. The largest sample size among the included studies was only 173. Most studies, however, concluded that the FVL polymorphism was an important risk factor for thrombosis in aPL positive or SLE patients.

Since the discovery of FVL as a risk factor for DVT in the general population, it's role in SLE and in aPL positive subjects has also been investigated. Initial results were inconsistent in reporting an association of FVL with thrombosis in SLE 27-30 however, extremely small sample sizes and infrequent event rates limited power to detect an association in these preliminary studies. Studies such as those included in our meta-analysis suggested that FVL was an important risk factor for thrombosis, however, these, too, had small sample sizes. Our meta-analysis confirms that, even when correcting for other known risk factors for thrombosis in SLE (of which aPL is the most well established), FVL plays an important role in thrombosis in SLE patients. Thus, patients with the FVL risk allele may constitute a subgroup of patients at higher risk of thrombosis than patients without this polymorphism. Because no significant interaction was found between the presence of the FVL polymorphism and aPL or other risk factors for thrombosis, the risk of FVL, as in the general population, appears to be additive rather than multiplicative. However, the lack of statistical interaction between FVL and aPL may have been due to a lack of power to detect

this interaction in our study. In addition, our results suggest that the presence of FVL appears to represent an independent risk factor for thrombosis in SLE that may increase risk beyond that attributable to other lupus-specific processes.

An interesting observation from our analyses is that the OR for the association between FVL and thrombosis in SLE is lower than that between FVL and thrombosis in the general population. Several reasons for this finding may exist. First, thrombosis occurs with a greater frequency and at a younger age in SLE patients than in the general population.31 Second, certain risk factors for thrombosis are more prevalent in SLE than in the general population. For example, SLE patients have a higher frequency of persistent aPL positivity, the most well-established risk factor for thrombosis in SLE. Finally, other factors that contribute to the higher risk of thrombosis in SLE include acquired SLE-specific risk factors (such as chronic inflammation) and acquired thrombosis triggers specific to this young, female age group (such as oral contraceptive use and pregnancy).32

The presence of more than one thrombosis risk factor has been shown to increase the risk of thrombosis in the general population. 9,33 Hudson et. al. demonstrated an association between the number of prothrombotic risk factors and a history of thrombotic events in subjects with aPL (OR 1.46 for each additional prothrombotic risk factor, 95% C.I. 1.003-2.134). In addition, the presence of more than one genetic risk factor has also been shown to increase thrombosis risk in the general population.9

Indeed, several studies included in this meta-analysis considered multiple genetic risk factors. In addition to FVL, another polymorphism that has been associated with increased thrombosis risk in the general population is the C677T polymorphism of the methyl tetrahydrofolate reductase (MTHFR) gene. This polymorphism is associated with elevated homocysteinemia. Furthermore, coinheritence of MTHFR with FVL likely increases the risk of venous thrombosis.33 Another such polymorphism is the 20210A prothrombin gene mutation, a G to A nucleotide transition at position 20210 of the 3' untranslated region of the prothrombin gene. 7 In addition to the FVL polymorphism, six studies10,14,16,19,23,26 considered the MTHFR polymorphism and eight studies10,14-16,18,19,25,26 considered the prothrombin gene mutation as risk factors for thrombosis. Most studies concluded that there was no association between MTHFR and prothrombin mutations and thrombosis, however, sample sizes were small and thus power may have been too low to detect a true association. Larger studies are needed to further study this issue in SLE subjects.

Limitations

Our primary meta-analysis was limited because we could not adjust for covariates that might help explain the association between FVL and thrombosis (such as the established thrombosis risk factor, aPL positivity). We therefore undertook a secondary analysis with individual patient level data in order to adjust for these important covariates in SLE as well as to analyze subgroups of thrombosis, such as DVT.

Because most of the studies included in our individual patient data meta-analysis were sampled on the basis of aPL positivity, selection bias may have occurred (oversampling patients with a tendency toward thrombosis). Our individual patient data analysis was also

limited because only five of a total of seventeen authors contributed individual-level patient data. However, by adding 1210 SLE subjects from the UCSF Lupus Genetics collection to this analysis, many of whom were aPL positive, we significantly increased the numbers of SLE subjects thus reducing these potential biases.

Conclusion and Future Directions

Our meta-analysis demonstrates that patients with SLE and/or aPL positivity who have the FVL polymorphism have at least two times the odds of thrombosis compared to patients without these risk factors. Future investigations should investigate the role of other genetic risk factors in the setting of SLE, such as the prothrombin and MTHFR mutations, as well as the combined effect of multiple risk factors on the risk of first and recurrent thromboses. With better risk characterization, we may be able to predict which SLE patients are at greatest risk for thrombosis and therefore be able to individualize treatment.

METHODS

Literature Search (Figure 1)

We searched the Cochrane Review Database31 to ensure that no similar prior reviews existed. The following Medical Subject Headings (MeSH) terms were searched in PubMed and EMBASE from 1993 (the year prior to the identification of FVL) until January 2007 in various combinations: lupus erythematosus, systemic OR systemic lupus erythematosus OR sle OR “primary antiphospholipid antibody syndrome” OR antiphospholipid syndrome, antibodies, antiphospholipid, factor V OR factor V Leiden OR “factor v leiden r506q polymorphism” OR “activated protein c resistance, thrombosis”. Searches were limited to studies involving human subjects.

Study Inclusion Criteria

Included studies confirmed subjects' SLE diagnosis according to the criteria defined by the American College of Rheumatology (ACR) 34, rigorously documented thrombotic events, included the FVL polymorphism as a primary risk factor for thrombosis, and included aPL as an important covariate.

Study Exclusion Criteria

Articles were first excluded based on non-English language as well as studies that only considered arterial thrombosis as the primary outcome (since FVL has been shown to be a risk factor for venous thrombosis), case reports, review articles, and studies that recruited all patients based on a positive thrombosis history (including primary antiphospholipid syndrome) since this precluded a comparison of FVL prevalence in patients with and without thrombosis.

Abstraction of Data

RK abstracted the data, JB was the second abstractor using the same standardized form, and LAC was the adjudicator.

Quality measures

Quality was judged based upon the above inclusion and exclusion criteria. This qualitative assessment was performed in lieu of a quality scoring scale because such scales have been shown to be incomplete and unreliable due to the heterogeneity between studies.35

Statistics

The unadjusted OR and 95% confidence interval (C.I.) for the association between the factor V Leiden polymorphism and thrombosis was the effect measure of interest and was calculated for venous and arterial thrombosis together (for cases) if not reported in the original article. Publication bias was assessed using a funnel plot and Egger's test.36 A Mantel-Haenszel test statistic was used to assess homogeneity, and data were combined using the Mantel-Haenszel method (fixed effects model) to obtain a summary estimate. STATA SE software, version 9.0 was used for these analyses (StataCorp, College Station, TX).

Individual Patient Data Meta-Analysis

Individual-level patient data was requested from authors of all studies included in this meta-analysis. Seven out of 17 authors responded to our request, and five contributed their data. To this individual-level patient data, we added data for 1210 European-American subjects in the UCSF Lupus Genetics Project.37 To enroll in this study, subjects completed an extensive questionnaire and gave permission for medical record review. The protocol was approved by the Institutional Review Board at UCSF. Details regarding subject recruitment and data collection are explained in a recent publication.11 Covariates considered in the individual patient data meta-analysis included the FVL polymorphism, age, gender, history of smoking, aPL status, and SLE status.

FVL genotypes for European-derived subjects from the UCSF Lupus Genetics Project were determined by an oligonucleotide ligation assay that combined PCR amplification of target sequences from 3 ng of genomic DNA with subsequent allele-specific oligonucleotide ligation. The ligation products of the two alleles were separated by hybridization to product-specific oligonucleotides, each coupled to spectrally distinct Luminex100 xMAP microspheres (Luminex, Austin, TX). The captured products were fluorescently labeled with streptavidin R-phycoerythrin (Prozyme, San Leandro, CA), sorted on the basis of microsphere spectrum, and detected by a Luminex100 instrument, as previously described.38

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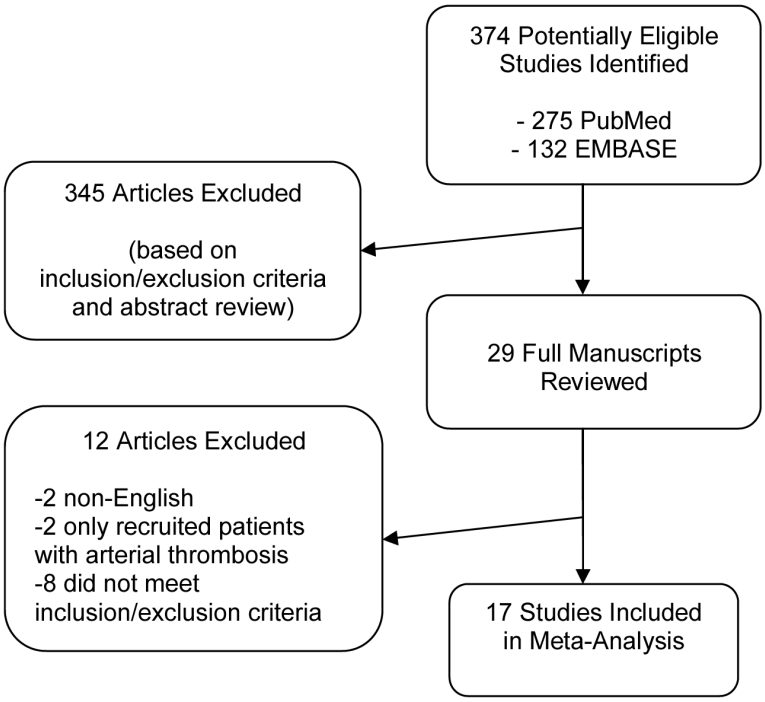
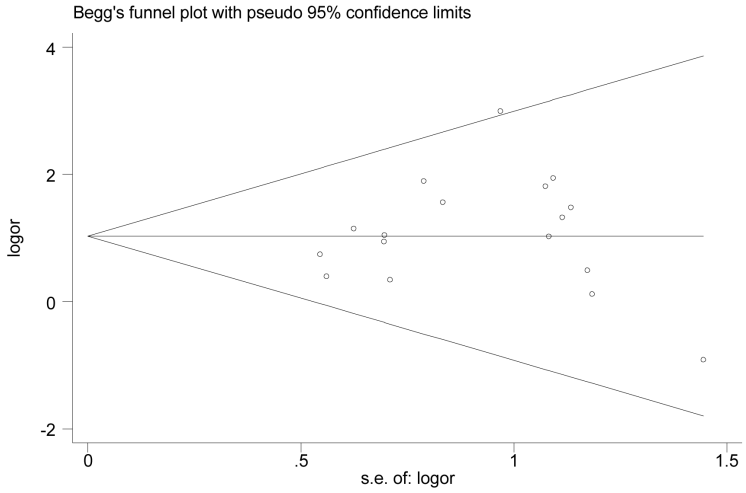


FIGURE 1.

Literature search strategy for meta-analysis of the factor V Leiden polymorphism and thrombosis among subjects with SLE and/or aPL positivity



logor = log of the odds ratio
s.e. of logor = standard error of the log of the odds ratio

FIGURE 2.

Funnel plot of 17 studies included in meta-analysis of the factor V Leiden polymorphism and thrombosis among subjects with SLE and/or aPL positivity

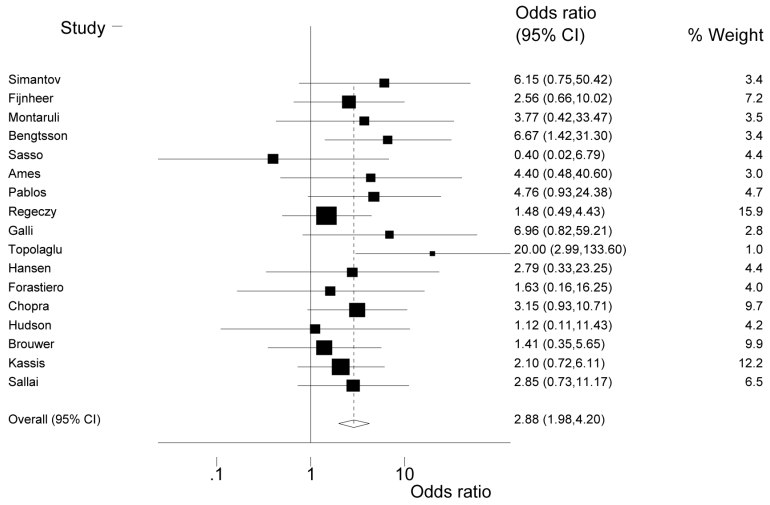


FIGURE 3. Forrest plot of 17 studies included in meta-analysis of the factor V Leiden polymorphism and thrombosis among subjects with SLE and/or aPL positivity

"%weight" calculated using Mantel-Haenzel method and fixed effects model

Square size represents contribution of each study to the meta-analysis (study weight)

TABLE 1

Summary of 17 studies included in meta-analysis of the factor V Leiden polymorphism and thrombosis among subjects with SLE and/or aPL positivity.

Author, Date[g]	Study location	Sample size (n) and enrollment criteria (SLE[a], aPL+[b], or both)	# SLE subjects	Ethnicity	# subjects with ACL[d] and/or LAC[e]	# FV+[c] and thrombosis +	# FV+ and thrombosis-	# FV- and thrombosis +	# FV- and thrombosis-	Crude Odds Ratios (with 95% Confidence Intervals)
Simantov[g] 1996	USA	150, both	97	European-derived African American Hispanic	LAC 3 ACL103	7	0	81	62	6.15 (0.782, 276.930)
Fijnheer 1996	Netherlands	173 SLE	All	Dutch (European-derived?)	LAC 43 ACL 94 Both 37	4	5	39	125	2.56 (0.48-12.49)
Montaruli 1996	Italy	60 aPL+	Not specified	Italian (European-derived?)	LAC 33 ACL 5 Both 12	5 (1 homozygous)	0	34	21	3.77 (0.41-181.2)
Bengtsson 1996	Sweden	78 SLE	All	Swedish (European-derived?)	LAC 13 ACL 26	5	3	14	56	6.67 (1.11 - 46.6)
Sasso 1997	USA	58 both	All	European-derived African-American	LAC 6 ACL 16 Both 34	1	1	40	16	0.4 (0.005 - 33.3)
Ames[g] 1998	England	49 aPL+	0	Not specified	LAC 5 ACL 4 Both 40	4	0	24	21	4.4 (0.43 - 217.4)
Pablos 1998	Spain	83 SLE+ and aPL+	83	Not specified	All had one or both	3	2	22	56	3.82 (0.40 - 47.72)
Regeczy 2000	Hungary	120 SLE	All	Hungarian (European-derived?)	LAC 4 ACL 48 Both 8	6	10	30	74	1.48 (0.40 - 4.96)
Galli 2000	Italy	152 aPL+	32	Italian (European-derived?)	128	5	0	91	56	3.72 (0.43 - 173.91)
Topaloglu 2001	Turkey	55 SLE	All	Not specified	ACL+ 21	4	3	3	45	20 (2.06 - 195.72)
Hansen[g] 2001	USA	99 aPL+	25	European-derived African-American 2 Other	All	8	0	70	21	2.79 (0.35 - 127.69)
Forastiero 2001	Argentina	105 aPL+	14	European-derived	LAC 22 ACL 29 Both 54	2	0	67	36	1.63 (0.13 - 87.97)
Chopra 2002	Canada	157 aPL+	124	Not specified	ACL147 LAC 69 Both 59	9	4	60	84	3.15 (0.83 - 14.56)
Hudson[g] 2003	Canada	87 aPL	26	European-derived African-American Hispanic Asian Other	ACL 67 LAC 20 B2G[f]22	1	3	19	94	1.65 (0.03 - 21.74)
Brouwer 2004	Netherlands	144 SLE	144	Not specified	ACL 12 LAC 11 Both 3	3	8	26	107	1.54 (0.25 - 7.00)

Author, Date[g]	Study location	Sample size (n) and enrollment criteria (SLE[a], aPL+[b], or both)	# SLE subjects	Ethnicity	# subjects with ACL[d] and/or LAC[e]	# FV+[c] and thrombosis +	# FV+ and thrombosis-	# FV- and thrombosis +	# FV- and thrombosis-	Crude Odds R (with 95% Confidence Intervals)
Kassis[g] 2004	Canada	415 aPL	85	European-derived Non-European-derived	APA+ 75 APA - 340 (included B2G	5	13	64	333	2.00 (0.54 - 6.2
Sallai 2007	Hungary	105 SLE	All	Not specified	ACL 22 LAC 37 Both 24 B2G 27	4	6(1 homozygo us)	18	77	2.85 (0.53 - 13.

[a] SLE = Systemic Lupus Erythematosus

[b] aPL = antiphospholipid antibody

[c] Factor V Leiden polymorphisms were heterozygous unless otherwise noted

[d] ACL = anticardiolipin

[e] LAC = lupus anticoagulant

[f] B2G = beta - 2 - glycoprotein

[g] These studies were also included in the secondary analyses

TABLE 2

Individual Patient Data Meta-Analysis Multivariate Results for Association with Thrombosis in European-derived Subjects

Covariate (n = 1309)	**# subjects**	**OR**	**p**	**95% C.I.**
Age (per 10 years)	1309	1.20	**2.29×10^{-4}**	1.09 - 1.33
Female gender	1241	0.44	**9.66×10^{-6}**	0.30 - 0.63
Factor V Leiden	93	1.91	**0.01**	1.16 - 3.16
Ever smoker	514	1.38	**0.02**	1.05 - 1.82
aPL positivity[a]	542	4.54	**$<10^{-9}$**	3.45 - 5.97
SLE	1020	1.26	0.14	0.93 - 1.71
SLE subjects only (n = 929)				
Age (per 10 years)	1309	1.29	**5.48×10^{-5}**	1.14 - 1.46
Female gender	917	0.71	0.20	0.42 - 1.20
Factor V Leiden	70	1.76	**0.05**	0.99 - 3.12
Ever smoker	389	1.23	0.20	0.89 - 1.71
aPL positivity	342	4.05	**$<10^{-9}$**	2.92 - 5.61

[a] aPL = antiphospholipid antibodies (anti-cardiolipin (ACL) IgM or IgM or lupus anticoagulant (LAC) positive at least once)

TABLE 3

Sensitivity analyses for individual patient data for association of the factor V Leiden polymorphism with venous thrombosis and deep venous thrombosis (DVT) in European-derived Subjects with SLE

Venous thrombosis (n = 936)	**OR**	***p***	**95% C.I.**
Age (per 10 years)	1.03	0.74	0.85 - 1.26
Female gender	0.46	**0.03**	0.23 - 0.91
Factor V Leiden	3.18	**0.001**	1.60 - 6.35
Ever smoker	1.22	0.44	0.73 - 2.04
aPL positivity[a]	4.49	**4.97×10^{-9}**	2.71 - 7.43
DVT (n = 942)			
Age (per 10 years)	1.01	0.89	0.83 - 1.23
Female gender	0.47	**0.04**	0.23 - 0.96
Factor V Leiden	2.33	**0.03**	1.09 - 4.92
Ever smoker	1.22	0.44	0.74 - 2.03
aPL positivity	4.19	**$<10^{-9}$**	2.54 - 6.91

[a] aPL = antiphospholipid antibodies (anti-cardiolipin (ACL) IgM or IgM or lupus anticoagulant (LAC) positive at least once)

TABLE 4

Individual Patient Data Meta-Analysis Bivariate Results for Association with Thrombosis in European-derived Subjects

Covariate	OR	p	95%C.I.
Age per 10 yrs	1.12	0.07	0.99 - 1.27
Female gender	0.34	1.37×10^{-5}	0.21 - 0.57
Factor V Leiden	2.34	0.01	1.13 - 5.01
Ever smoker	1.62	0.01	1.08 - 2.42
SLE	0.74	0.09	0.51 - 1.06
SLE subjects only			
Age per 10 yrs	1.19	2×10^{-3}	1.06 - 1.32
Female gender	0.67	0.10	0.40 - 1.13
Factor V Leiden	1.81	0.02	1.05 - 3.06
Ever smoker	1.16	0.33	0.85 - 1.58
aPL positivity[a]	2.84	1.02×10^{-12}	2.11 - 3.82

[a] aPL = antiphospholipid antibodies (anti-cardiolipin (ACL) IgM or IgM or lupus anticoagulant (LAC) positive at least once)