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The Association of α-Fibrinogen Thr312Ala polymorphism and Venous Thromboembolism in the LITE study

Laura J. Rasmussen-Torvik[1], **Mary Cushman**[2], **Michael Y. Tsai**[3], **Yan Zhang**[3], **Susan R. Heckbert**[4], **Wayne D. Rosamond**[5], and **Aaron R. Folsom**[1]

1 *Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN, 55454*

2 *Department of Medicine, University of Vermont College of Medicine, Burlington, VT, 05401*

3 *Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455*

4 *Department of Epidemiology, University of Washington, Seattle, WA, 98101*

5 *Department of Epidemiology, University of North Carolina-Chapel Hill, Chapel Hill, NC, 27514*

Abstract

Introduction—The α-fibrinogen Thr312Ala variant has been shown to influence clot structure through increased factor XIII cross-linking and formation of thicker fibrin fibers. However, the effect of this common variant on risk of venous thromboembolism (VTE) is unclear. This paper reports the association between the Thr312Ala variant and VTE in the LITE study.

Materials and Methods—506 cases and 1014 controls frequency matched on age, sex, race, and study were drawn from two prospective studies and included in the analysis. Logistic regression was used to examine the association between the Thr312Ala and VTE.

Results—In a logistic regression model minimally adjusted for the matching variables, the Thr312Ala TA and AA genotypes were associated with a significantly higher risk of VTE than the TT genotype [TA odds ratio (OR) and 95% confidence interval 1.27 [1.01–1.60], AA OR 1.49 [1.00–2.22]. Associations were similar in analyses of PE and DVT considered separately and across racial and study subgroups. The association between α-fibrinogen Thr312Ala and VTE was modified by both BMI and the FXIII Val34Leu variant; the combination of elevated BMI or FXIII Val34Leu with α-fibrinogen Thr312Ala conveyed lower odds of VTE than would be expected by an additive or multiplicative model of individual risk factors.

Conclusions—These results suggest that α-fibrinogen Thr312Ala is involved in the pathogenesis of VTE and that its action may be modified by other VTE risk factors.

Keywords

deep vein thrombosis; fibrinogen; polymorphism

Corresponding Author: Aaron Folsom, MD, Division of Epidemiology and Community Health, University of Minnesota School of Public Health, 1300 S. Second St, Suite 300, Minneapolis, MN 55454-1015, Tel: 612-626-8862, Fax: 612-624-0315, Email: E-mail: folsom@epi.umn.edu.

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common, life-threatening disease. The Longitudinal Investigation of Thromboembolism Etiology (LITE) reported a VTE incidence of 2 per 1000 person years in middle aged and older adults and those subjects experiencing a first incidence of VTE had a 28 day case fatality rate of 11%.[1] Despite the incidence and severity of VTE, the etiology of VTE is incompletely understood. Known risk factors for VTE include cancer, immobilization, surgery, trauma, pregnancy and coagulation abnormalities.[2] The LITE study reported that age, race, sex, BMI, and diabetes were associated prospectively with VTE occurrence, but other common cardiovascular risk factors such as smoking, dyslipidemia, physical inactivity and alcohol consumption were not associated with VTE in this cohort.[3]

To better understand the etiology of VTE, some groups have investigated plasma fibrinogen as a risk factor for VTE with conflicting results. In the Leiden Thrombophilia Study, a case-control study, higher plasma fibrinogen level was associated with increased risk of deep vein thrombosis[4], but in the LITE study fibrinogen was not associated with VTE[5]. Studies have also examined genetic variation in the proteins encoding fibrinogen. One variant of interest is the Thr312Ala α-fibrinogen amino acid substitution (6534AG). Thr312Ala has been shown to impact clot structure and properties by increasing Factor XIII cross-linking and formation of thicker fibrin fibers[6], but not to impact circulating levels of fibrinogen.[7] Thr312Ala is very common with a minor allele frequency of 23% in a UK sample.[8] α-fibrinogen Thr312Ala was associated with PE in a case control study of UK patients, although the association did not remain significant after adjustment for age, sex, malignancy, Factor V Leiden, and the Factor XIII Val34Leu variant.[8] α-fibrinogen Thr312Ala was also significantly associated with VTE in a case control study of Taiwanese patients[9] and associated with combined arterial and venous thrombosis in a cohort of Turkish children.[10] No studies have yet reported the association of α-fibrinogen Thr312Ala with VTE in an African American Study population.

To better understand the relation between α-fibrinogen Thr312Ala and VTE, we studied this association in the LITE study, a population based-study of the incidence and risk factors for VTE. In addition, because of the large number of events in the LITE study, we were able to examine the association of α-fibrinogen Thr312Ala with specific subtypes of VTE (such as incident or recurrent VTE, idiopathic or secondary VTE, and DVT alone vs. PE and DVT). We also examined the association of α-fibrinogen Thr312Ala and VTE in the presence and absence of several other risk factors for VTE.

Materials and Methods

Subjects

Subjects for the LITE study were participants of two prospective cohort studies, the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) study. The details of the LITE, ARIC and CHS studies have been published previously.[1,3, 11,12] Briefly, 15,792 ARIC participants were recruited in 1987–1989, 5201 CHS participants were recruited in 1989–1990, and 687 additional African American CHS participants were recruited in 1992–1993. Participants were assessed for cardiovascular risk factors at baseline and plasma and DNA samples were stored. Each study maintained contact with all participants and identified all hospitalizations. Potential cases of hospitalized VTE were identified in a first phase through 1998 [1] and in a second phase through 2002. Hospital records were copied, and VTEs were validated by review by two physicians. In most instances, definite DVT events had a positive duplex ultrasound or venogram, and probable DVT events typically had a positive Doppler ultrasound or impedance plethysmography. Definite PE was based on ventilation/perfusion imaging, computed tomography, or autopsy. Both probable and definite cases were considered together for analysis.

To investigate risk factors for VTE, a nested case control sample was created. Methods of the phase 1 sample were published previously[13] and repeated in phase 2. All VTE cases were included through the end of 2002 in CHS and through mid-2003 in ARIC. Controls were randomly chosen using incidence density sampling from the ARIC and CHS cohorts at a ratio of approximately 2 controls per case and frequency matched to cases according to age, gender, race, and study of origin. In total, 548 VTE cases and 1097 controls were selected (with 8 individuals being counted as both a case and a control for an earlier case).

Laboratory methods

Stored blood samples drawn in the fasting state at baseline were used. Fibrinogen and Factor VIII were measured at baseline in ARIC and CHS as previously described.[5] Diabetes was classified based on serum glucose measurements, use of hypoglycemic medication, or self-report of diabetes diagnosis, as previously described.[3] α-Fibrinogen Thr312Ala (encoded by a A to G base change at position 6543) was determined using the multiplexing capability of the MassARRAY homogenous MassEXTEND assay of the Sequenom system (San Diego, CA 92121). The polymorphism was genotyped using Sequenom forward and reverse primers 5′-ACGTTGGATGAGCTCCCAGAGTTCCAGC-3′ and 5′-ACGTTGGATGAGGGACTGCAACCTGGAAAC-3′, respectively; the extension primer was 5′-GCTCTGGACCTGGAAGT-3′. FXIII Val34Leu and β-fibrinogen -455G/A were typed as previously described.[14,15]

Study Population

Individuals (n= 48, 16 cases and 32 controls) who did not consent to DNA analysis were not studied. An additional 71 individuals (23 cases and 48 controls) were excluded because they could not be successfully genotyped for α-fibrinogen Thr312Ala, and six individuals (three cases and three controls) were excluded because they did not self-report black or white race. The excluded and included individuals did not differ significantly on any baseline variables except for self-reported race. After these exclusions there were 1520 individuals included in this analysis, 506 cases and 1014 controls.

Statistical Analysis

All statistical analyses were performed using PC SAS v 9.1 (SAS Institute Inc. Cary, NC). The association of α-fibrinogen Thr312Ala with established risk factors for VTE was assessed using χ^2 analysis and ANOVA. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95 % C.I.s of VTE in relation to the α-fibrinogen polymorphism represented as a two degree of freedom variable. All logistic regression analyses were adjusted for levels of the frequency matching variables. To assess confounding and effect modification by the FXIII Val34Leu and β-fibrinogen -455G/A, these SNPs were included in regression models as one degree of freedom variables; individuals with VL and LL genotypes for FXIII were grouped together as were participants with β-fibrinogen -455 GA and AA genotypes. Logistic regression analyses with case subtype subgroups were performed using all controls in the comparison group. To test for effect modification on a multiplicative scale, 2 degree of freedom interaction terms were included in logistic regression models adjusted for matching variables. For variables where multiplicative effect modification was detected, expected joint effects with α-fibrinogen Thr312Ala were calculated using the formula $[OR_1 + OR_2 - 1]$ for the additive models and the formula $[OR_1 * OR_2]$ for the multiplicative models where OR_1 and OR_2 are odds ratios for the individual risk factors. Estimates of linkage disequilibrium were obtained using the Haploview program.[16]

Results

Of the 506 validated VTE events included, 59 (11.7 %) self-reported a history of VTE at baseline. 351 cases had DVT only, 85 had PE only, and 70 were cases were found to have both. 218 cases (43.1%) were idiopathic (not occurring within 90 days of major trauma, surgery, marked immobility, active cancer or chemotherapy). Table 1 shows the baseline characteristics of cases and controls used in this analysis. As reported previously[3,5,13], cases were more likely to have diabetes, more likely to have the Factor V Leiden mutation and had higher plasma Factor VIII coagulant activity than controls.

Table 2 shows the distribution of Thr312Ala genotypes in cases and controls. The SNP was found to be in Hardy-Weinberg equilibrium in both races, but the frequency of the genotypes differ significantly between the races; the minor allele frequency of the SNP was higher in blacks (0.33) compared to whites (0.23).

Table 3 shows the ORs and 95% C.I. of VTE by α-fibrinogen Thr312Ala genotype. Because of the nested case-control design used, all covariates were measured at baseline. In a model minimally adjusted for the matching variables, Thr312Ala was significantly associated with VTE at the $p < .05$ level, with the TA (OR = 1.27) and AA (OR= 1.49) genotypes conferring greater risk of VTE than the most common TT genotype. When Thr312Ala was modeled as a dichotomous variable, the combined TA and AA genotypes were associated with a greater risk of VTE than the TT genotype (OR = 1.31 p = .014). To determine which variables might confound this relationship, the associations of Thr312Ala with plasma fibrinogen level, Factor V Leiden, β-fibrinogen -455 G/A SNP, FXIII Val32Leu, diabetes status, BMI, and plasma FVIII level were examined. Of these factors only the β-fibrinogen -455 G/A SNP was significantly associated with α-fibrinogen Thr312Ala. Plasma fibrinogen level was not significantly associated with Thr312Ala (after adjustment for matching variables TT genotype mean plasma fibrinogen level: 317 mg/dl, TA genotype mean plasma fibrinogen level: 309 mg/dl, AA genotype mean plasma fibrinogen level: 316 mg/dl). To verify the association between β-fibrinogen -455 G/A and α-fibrinogen Thr312Ala, we calculated the linkage disequilibrium (LD) between them using both D′ and r^2. Among the whites in the study population the r^2 measure between α-fibrinogen Thr312Ala and β-fibrinogen -455 G/A was .021 and the D′ measure was .491, among blacks the r^2 measure was .023 and the D′ measure was 0.85, suggesting that the two SNPs were in very low linkage disequilibrium. With adjustment for β-fibrinogen -455 G/A SNP in the regression analysis, the ORs for the Thr312Ala changed only slightly. Further controlling for other risk factors for VTE did not change the odds ratio for the TA genotype (OR = 1.23), and increased the odds ratio for the AA genotype to 1.64 (p=0.047).

Race, study, diabetes status, BMI, fibrinogen and Factor VIII levels, Factor V Leiden, β-fibrinogen -455 G/A SNP, and FXIII Val32Leu, were also investigated as possible multiplicative effect modifiers of the Thr312Ala/VTE relationship. Only BMI (interaction p-value 0.041) and FXIII Val34Leu (interaction p-value 0.046) were found to be significant modifiers on a multiplicative scale.

Table 4 lists the odds ratios and 95% confidence intervals of VTE by Thr312Ala genotype for various pre-specified subgroups. Across both studies (ARIC and CHS) and self-reported race groups, a similar pattern of odds ratios was seen, with Thr312Ala TA and AA genotypes being generally associated with higher odds of VTE than the TT genotype. This trend was also seen across different subtypes of VTE.

Joint associations with VTE for Thr312Ala with FXIII Val34Leu, BMI, and Factor V Leiden are presented in table 5. The combination of elevated BMI or FXIII Val34Leu with α-fibrinogen Thr312Ala conveyed lower odds of VTE than would be expected by an additive or

multiplicative model of individual risk factors. The combination of Factor V Leiden and α-fibrinogen Thr312Ala conveyed higher odds of VTE than would be expected on an additive scale but did not depart substantially from expected values on the multiplicative scale.

Discussion

In this study we found that the Thr312Ala alanine variant was associated with an increased risk of VTE compared to the threonine variant with unadjusted ORs of 1.27 for individuals with one copy of the alanine variant and 1.49 for individuals with two copies of the alanine variant. These results are similar to previously published results which showed the alanine variant to be associated with increased odds of PE in a British population, VTE in a Taiwanese population[8,9] and increased odds of postoperative thrombosis in Turkish children[10].

As expected, the association between α-fibrinogen Thr312Ala and odds of VTE was not substantially confounded by several other VTE risk factors, as most of these confounders were not associated with Thr312Ala. However, the association was slightly confounded by the β-fibrinogen -455 G/A SNP because this SNP, itself a significant predictor of VTE in this population (Mary Cushman, personal communication), was in slight linkage disequilibrium with the α-fibrinogen Thr312Ala. The linkage between these two SNPs might be expected given the physical proximity of the two genes (within approximately 20,000 bp on chromosome 4q28). A study in the Taiwanese population found the measure of D′ between the two SNPs to be about .45, similar to the measure of D′ in the white population of this study (.49). This result highlights the importance of considering other putative functional fibrinogen variants in genetic analyses of fibrinogen polymorphisms, given the tight clustering of fibrinogen genes on chromosome 4q28. An analysis in the Leiden Thrombophilia Study has suggested that significant associations seen with α-fibrinogen SNPs and VTE are due entirely to linkage disequilibrium with SNPs in the γ-fibrinogen gene.[17] However, a similar study in the Taiwanese population concluded that SNPs in the α-fibrinogen were associated with susceptibility to VTE.[9]

We chose to use a model-free 2 degree of freedom approach to test the significance of the association between Thr312Ala and VTE. Assuming, instead, a dominant model of inheritance (where TA and AA genotypes are assumed to confer identical odds of VTE) resulted in smaller p-values for association tests than shown in Tables 3 and 4, but the pattern of ORs observed suggests that this model of inheritance is not appropriate. Although there is some variability in the OR seen in subgroup analyses, the uniform direction of the ORs, with the A allele consistently inferring greater odds of VTE that the T allele, lends credence to the role of the alanine allele in increasing VTE risk.

Previous epidemiological and in-vitro studies have examined the mechanism through which the Thr312Ala may impact VTE risk. In vitro studies have shown that Ala312 clots have thicker fibers and more α–chain crosslinking than Thr312 clots[6], and epidemiological studies have found that α–fibrinogen Thr312Ala is not associated with plasma fibrinogen[7], suggesting that the Thr312Ala variant influences function, but not circulating level of α–fibrinogen. Our results support this interpretation, as plasma fibrinogen was not significantly associated with Thr312Ala, and the inclusion of plasma fibrinogen level in a logistic regression model of VTE did not change the estimates of effect for the α–fibrinogen Thr312Ala genotypes.

We observed two significant effect modifiers to the α–fibrinogen Thr312Ala and VTE relationship: obesity and Factor XIII Val34Leu polymorphism. The combination of elevated BMI (greater than 30 kg/m^2) with α-fibrinogen Thr312Ala conveyed lower odds of VTE than would be expected by either an additive or multiplicative model of individual risk factors. One explanation for this modification of effect may be that obesity and Thr312Ala increase VTE

risk through related mechanisms and thus the combination of these risk factors does not substantially increase risk compared to either individual risk factor. There may be a similar explanation for the observed negative interaction between FXIII Val34Leu and α-fibrinogen Thr312Ala. The effect modification we observed between FXIII Val34Leu and α-fibrinogen Thr312Ala was different from findings in an earlier British study of VTE. In that study, the TT Thr312Ala genotype only conferred decreased PE risk among individuals possessing at least one Leu allele for FXIII.[8] Given these conflicting results, and the fact that the Ala312 variant has been shown to increase Factor XIII cross-linking of clots in vitro, the effect modification of FXIII Val34Leu on α–fibrinogen Thr312Ala and VTE should be investigated in other studies. Factor V Leiden was not found to be an effect modifier on the multiplicative scale but did appear to have a larger than expected joint effect with Thr312Ala on the additive scale, suggesting that the Thr312Ala variant might prove to be of particular importance to individuals with Factor V Leiden

This investigation has several strengths. Because of the large size of the LITE cohort, we had good power to detect associations in the cohort as a whole and in several subgroups. We also could control for several other VTE risk factors in our analysis. The inclusion of African Americans in the LITE study sample allowed us to report on the association of α–fibrinogen Thr312Ala genotype and VTE in African Americans for the first time. One limitation of this study was the relatively small number of African Americans in this analysis.

In conclusion, we found that the common α–fibrinogen Thr312Ala variant was a modest risk factor for VTE in the LITE cohort. The association of Thr312Ala with VTE appeared to be additive, with each copy of the alanine genotype conferring additional risk of VTE. The association was weaker in those with higher BMI and was also modified by the Factor XIII Val34Leu variant. In the future, this association needs to be verified in other ethnic groups, and the interaction between α–fibrinogen Thr312Ala and FXIII Val34Leu more fully explored.

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Abbreviations

VTE
: venous thromboembolism

DVT
: deep vein thrombosis

PE
: pulmonary embolism

LITE
: The Longitudinal Investigation of Thromboembolism Etiology

CHS
: Cardiovascular Health Study

ARIC

Atherosclerosis Risk in Communities

OR

odds ratio

LD

linkage disequilibrium

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Table 1

Baseline characteristics of venous thromboembolism cases and controls, LITE

Risk Factor	Controls (n = 1014)	Cases (n = 506)
Age (years)*	62.5 (10.1)	62.6 (9.8)
Male (%)*	43.9	44.5
Race (%)*		
Black	26.4	26.7
White	73.6	73.7
Study (%)*		
ARIC	61.9	62.5
CHS	38.1	37.5
Diabetes (%)	11.5	17.6
Factor V Leiden (%)	3.3	10.3
BMI (kg/m^2)	27.5 (5.0)	29.0 (5.6)
Fibrinogen (mg/dl)	314 (67)	312 (65)
Factor VIIIC (%)	128 (39)	146 (50)

Means are given ± SD

*matching variables

Table 2

Frequencies (%) of α-fibrinogen Thr312Ala genotype in venous thromboembolism cases and controls, by self-reported race, LITE

Genotype	TT	TA	AA
Cases			
White	192 (51.8)	147 (39.6)	32 (8.6)
Black	52 (38.5)	67 (49.6)	16 (11.9)
Controls			
White	432 (57.9)	276 (37.0)	38 (5.1)
Black	124 (46.3)	108 (40.2)	36 (13.5)

Table 3

Odds ratio and 95% confidence interval of venous thromboembolism in relation to α–fibrinogen Thr312Ala genotype, LITE

	Genotype			
Model	**TT (referent)**	**TA**	**AA**	**p-value***
Model 1†	1.0	1.27 [1.01–1.60]	1.49 [1.00–2.22]	.037
Model 2‡	1.0	1.23 [0.98–1.54]	1.41 [0.94–2.11]	.097
Model 3§	1.0	1.23 [0.96–1.57]	1.64 [1.06–2.55]	.047

* for a 2 degree of freedom test

† Model adjusted for matching variables (age, sex, race, study)

‡ Model adjusted for matching variables plus β-fibrinogen -455G/A SNP

§ Model adjusted for matching variables, β-fibrinogen -455G/A SNP, Factor V Leiden, Factor VIIIC, fibrinogen, BMI

Table 4

Subgroup odds ratios and 95% confidence intervals of venous thromboembolism by α–fibrinogen Thr312Ala genotype, LITE

Subgroup	Cases (n)	Controls (n)	Odds ratio (95% C.I.) by genotype			p-value*
			TT (referent)	TA	AA	
Study						
ARIC†	316	628	1.0	1.13 [0.85–1.51]	1.74 [1.02–2.94]	.116
CHS†	190	386	1.0	1.60 [1.10–2.32]	1.26 [0.68–2.32]	.048
Race						
Black‡	135	268	1.0	1.50 [0.96–2.35]	1.05 [0.53–2.05]	.184
White‡	371	746	1.0	1.20 [0.92–1.56]	1.92 [1.16–3.18]	.028
Case subgroups						
PE§	155	1014	1.0	1.04 [0.72–1.50]	1.85 [1.05–3.25]	.094
DVT§	421	1014	1.0	1.41 [1.11–1.79]	1.52 [1.00–2.33]	.0094
Both PE and DVT§	70	1014	1.0	1.56 [0.92–2.66]	2.55 [1.20–5.42]	.038
Idiopathic VTE§	218	1014	1.0	1.26 [0.92–1.72]	1.78 [1.06–2.97]	.062
Secondary VTE§	288	1014	1.0	1.29 [0.98–1.70]	1.29 [0.78–2.14]	.174

*for a 2 degree of freedom test

†adjusted for age, sex, race

‡adjusted for age, sex, study

§adjusted for age, sex, race, study

Table 5

Joint odds ratios and 95% confidence intervals of venous thromboembolism by α–fibrinogen Thr312Ala genotype and effect modifiers, LITE

Joint risk factor contributors		Cases (n)	Controls (n)	OR (95% C.I.)*	Expected OR Additive Model	Expected OR Multiplicative Model
α–fibrinogen Thr312Ala genotype	FXIII Val34Leu genotype					
TT	VV	126	308	1 (reference)		
TT	VL+ LL	116	247	1.14 (0.84–1.54)		
AT + AA	VV	160	269	1.45 (1.09–1.93)		
AT + AA	VL + LL	97	189	1.27 (0.92–1.76)	1.59	1.65
α–fibrinogen Thr312Ala genotype	BMI (kg/m^2)					
TT	≤ 30	142	425	1 (reference)		
TT	> 30	100	130	2.39 (1.72–3.34)		
AT + AA	≤ 30	166	338	1.49 (1.14–1.95)		
AT + AA	> 30	91	120	2.30 (1.61–3.28)	2.88	3.56
α–fibrinogen Thr312Ala genotype	Factor V Leiden †					
TT	No	214	535	1 (reference)		
TT	Yes	28	20	3.60 (1.97–6.58)		
AT + AA	No	233	445	1.30 (1.04–1.63)		
AT + AA	Yes	24	13	4.67 (2.32–9.39)	3.90	4.68

*odds ratios adjusted for age, sex, race, study

†includes individuals heterozygous and homozygous for Factor V Leiden