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Rosendaal, F.R.

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Alexander P Reiner [1,2] Michele B Frank [1] Stephen M Schwartz [2,3] Michael L Lindenberger [1] W T Longstreth Jr [3,4] Gayle Lemaitre [1] Fritis R Rosendaal [5] Bruce M Psaty [1,2] and David S Siscovick [1,2]
Departments of [1]Medicine and [2]Epidemiology University of Washington [3]Fred Hutchinson Cancer Research Center, [4]Department of Neurology University of Washington Seattle WA USA and [5]The Hemostasis and Thrombosis Research Center and Department of Clinical Epidemiology Leiden University Medical Center The Netherlands

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Summary The inconsistent findings among association studies that have examined the relationship between factor XIIIA Val34Leu and thrombosis may be owing to (1) population differences in the prevalence of other risk factors that modify the association with Val34Leu or (2) linkage disequilibrium with other functional factor XIIIA polymorphisms We therefore performed genotyping for factor XIIIA Val34Leu Tyr204Phe and Pro564Leu in a population-based study of myocardial infarction (MI) and ischaemic stroke among white women <45-years of age and 345 demographically similar controls and examined potential interactions with other risk factors The presence of the factor XIIIA Leu34 allele was associated with a slight decreased risk of MI [odds ratio (OR) = 0 80] that was most pronounced among women with traditional cardiovascular risk factors Paradoxically women carrying two copies of the Leu34 allele had a nearly fourfold increased risk of ischaemic stroke relative to the Val34/Val34 genotype Heterozygosity for factor XIIIA Phe204 was associated with a milder increased risk of ischaemic stroke and analysis of a kindred with congenital dysfibrinogenaemia suggested that co-inheritance of the factor XIIIA Phe204 allele may increase susceptibility to ischaemic stroke Our results suggest that the factor XIIIA Val34Leu variant may be associated with a decreased risk of MI among young women with other risk factors The relationship of factor XIIIA polymorphisms to cerebrovascular disease requires further study

Keywords: factor XIII myocardial infarction stroke thrombo-embolic disease

Coagulation factor XIII circulates as a tetramer composed of two catalytic A subunits and two carrier B subunits and participates during the final step of the coagulation cascade Thrombin cleavage of a 37-amino-acid N-terminal peptide from factor XIIIA results in formation of activated factor XIII a transglutaminase that forms γ-glutamyl-ε-lysyl bonds between adjacent fibrin molecules The intermolecular cross-linking of fibrin as well as the cross-linking of α_2-antiplasmin to the fibrin clot by activated factor XIII increases clot stability and resistance to fibrinolysis (Muszbek *et al* 1999)

A common Val34Leu polymorphism of the factor XIIIA subunit results in an accelerated rate of conversion of factor XIII to activated factor XIII by thrombin and an altered cross-linked fibrin clot structure (Ariens *et al* 2000 Balogh *et al* 2000 Trumbo & Maurer 2000 Wartiovaara *et al* 2000) In some epidemiological studies the Leu34 allele has been associated with decreased risk of myocardial infarction (MI) (Kohler *et al* 1998 Wartiovaara *et al* 1999 Franco *et al* 2000) and ischaemic stroke (Elbaz *et al* 2000) but other studies have found no association (Canavy *et al* 2000 Corral *et al* 2000) We hypothesized two possible reasons for these inconsistent findings First the association of factor XIIIA Val34Leu with decreased risk of arterial thrombotic disease may be demonstrable only within certain populations such as younger individuals or those with other genetic or acquired risk factor(s) that operate at least in part through the coagulation/fibrinolytic system Second Val34Leu is in partial linkage disequilibrium with other factor XIIIA coding sequence polymorphisms (Kohler *et al* 1999a Reiner *et al* 2001a) that contribute to phenotypic variation in factor XIII (Anwar *et al* 1999 Gallivan *et al* 1999 Sahi *et al* 2000) Thus association studies that examine only Val34Leu do not account for the possible confounding effects of these other factor XIIIA variants

Correspondence Alexander P Reiner MD Cardiovascular Health Research Unit 1730 Minor Avenue Suite 1360 MR9 Box 358080 Seattle WA 98101-1448 USA E-mail apreiner@u.washington.edu

To test these hypotheses we examined the association between three functional factor XIIIA polymorphisms (Val34Leu Tyr204Phe and Pro564Leu) and the risk of MI and ischaemic stroke in women under 45 years of age As we previously demonstrated the potential importance of the interactions between several inherited prothrombotic variants (factor V Arg506Gln prothrombin G20210A platelet glycoprotein IIb Ile843Ser and platelet glycoprotein Ia C807T) and traditional cardiovascular risk factors in this study population (Rosendaal *et al* 1997a b Reiner *et al* 2000 2001b) we also explored the factor XIIIA polymorphisms in the context of gene environment and gene–gene interaction

PATIENTS AND METHODS

Study subjects and data collection Because of the rare occurrence of arterial thrombotic disease in young women we designed a population-based case–control study that included two case groups (acute MI and ischaemic stroke) compared with demographically similar control subjects free of cardiovascular or cerebrovascular disease (Rosendaal *et al* 1997a b) The study population consisted of women 18–44 years of age residing in three contiguous counties in western Washington state between 1991 and 1995 which represented approximately 2 2 million women-years at risk MI and ischaemic stroke cases were initially identified by chart review of discharge diagnoses from all 34 hospitals and emergency medical service incident reports in the study region The diagnosis of MI was based on symptoms electrocardiographic changes and elevated cardiac enzymes Stroke was defined as new focal neurological deficit(s) with no other apparent cause lasting > 24 h and the classification of arterial ischaemic stroke was based on review of brain imaging studies and lumbar puncture results by the study neurologist Six hundred and eighty-four eligible control subjects identified by random digit dialling were frequency matched to the age distribution of the cases

Of the eligible study subjects 107 out of 161 (66 5%) patients with non-fatal MI 58 out of 84 (75 3%) patients with non-fatal ischaemic stroke and 526 out of 684 (76 9%) eligible control subjects were willing to participate in an in-person interview which involved ascertainment of demographic characteristics and traditional cardiovascular risk factors Smokers were defined as subjects who reported smoking both currently and regularly (at least five cigarettes per week for at least six consecutive months) Obesity was defined as body mass index (BMI) $\geq 27\ 3\ kg/m^2$ A woman was classified as hypertensive diabetic or hypercholesterolaemic if she reported ever receiving the diagnosis by a physician

Venous blood samples were collected into EDTA-treated vacutainers from a subset of the study participants (78 MI cases 41 ischaemic stroke cases and 391 participating control subjects) To minimize the possibility of confounding owing to population admixture we confined our analysis to the 68 MI cases 36 ischaemic stroke cases and 345 control subjects with blood samples who were white

Factor XIII genotyping Genomic DNA samples were prepared from blood leucocytes as described previously (Rosendaal *et al* 1997a b) Genotyping for the factor XIII Val34Leu Tyr204Phe and Pro564Leu polymorphisms the factor V Arg506Gln and prothrombin G20210A mutations and the platelet glycoprotein IIb Ile843Ser and glycoprotein Ia C807T polymorphisms were performed by polymerase chain reaction (PCR) amplification of genomic DNA followed by restriction fragment length polymorphism (RFLP) analysis as previously described (Rosendaal *et al* 1997a b Reiner *et al* 2000 2001a b) Laboratories performing the genotyping were blinded to the case or control status and other characteristics of the subjects from whom the samples were obtained

Statistical analysis The association of each factor XIII genotype with MI or stroke was examined by logistic regression adjusted for age and expressed as odds ratios (OR) and 95% confidence intervals (95% CI) (model A) Homozygosity for the common allele (i e Val34/Val34 Tyr204/Tyr204 or Pro564/Pro564) was used as the reference group in the regression models and the heterozygous and rare homozygous genotypes were modelled separately using dummy variables We also fitted a multivariate logistic model that included all three factor XIIIA polymorphisms simultaneously to adjust for potential confounding owing to linkage disequilibrium (model B) The extent to which associations with factor XIIIA genotypes were modified by other medical lifestyle or genetic cardiovascular risk factors were assessed through analyses stratified on these other risk factors In these subgroup analyses the three dummy variables representing the common homozygous heterozygous and rare homozygous genotypes were collapsed into a binary variable based on post hoc analysis of the data To test for the presence of interaction multiplicative terms were introduced into the logistic regression model and the *P*-value was computed for the likelihood ratio test comparing the model containing the interaction term with the model lacking the interaction term All statistical testing was two sided and performed at the $\alpha = 0\ 05$ level

Family study In a separate analysis we performed genotyping for the three factor XIIIA polymorphisms among 14 family members of a kindred with congenital dysfibrinogenaemia in whom a father and daughter had suffered ischaemic stroke at ages 57 and 42 years respectively This family was ascertained through a third family member who presented at age 40 years with recurrent venous thrombo embolic disease and was found to be heterozygous for a fibrinogen γ-chain Arg275Cys mutation (Lunenberger *et al* 2000) Informed consent was obtained for all family studies using protocols approved by the Human Subjects Committee at the University of Washington

RESULTS

Characteristics of the study subjects

The characteristics of the MI cases ischaemic stroke cases and control subjects are summarized in Table I The mean

Table I. Characteristics of myocardial infarction (MI) cases, ischaemic stroke cases and control subjects.

	MI cases $n = 68$	Ischaemic stroke cases $n = 36$	Control subjects $n = 345$
Age (years)			
Mean	39·8	37·9	37·7
Median	41·0	39·5	39·0
Range	23–44	21–44	19–44
Premenopausal (%)	89·7	91·7	95·9
Current oral contraceptive use (%)	4·4	11·4	10·9
Current smokers (%)	70·6	33·3	20·8
Obesity (%)	51·5	47·1	26·5
Hypertension (%)	35·3	33·3	9·7
Diabetes (%)	14·7	22·2	2·9
Hypercholesterolaemia (%)	38·2	8·3	15·7

age of the study subjects was 38·0 years, and ranged from 18 to 44 years. The majority of the women were premenopausal and were not current users of oral contraceptives. Traditional atherosclerotic risk factors such as smoking, obesity, hypertension and diabetes were more common among both MI patients and ischaemic stroke patients than controls. An increased prevalence of hypercholesterolaemia was confined to the MI cases.

Factor XIIIA polymorphisms and risk of MI

The proportion of individuals carrying at least one copy of the Leu34 allele was slightly lower among MI patients (39·7%) than among control subjects (45·8%) (Table II). However, the confidence intervals around the MI risk estimates for the Val34/Leu34 genotype (odds ratio, OR = 0·80) and the Leu34/Leu34 genotype (OR = 0·77) were compatible with the null hypothesis of no association (model A). As indicated in Table II model B, the estimates of MI risk associated with each Val34Leu genotype were essentially unchanged after multivariate adjustment for the factor XIIIA Tyr204Phe and Pro564Leu polymorphisms. The age-adjusted OR associated with carrying at least one copy of the Leu34 allele compared with the Val34/Val34 genotype was 0·80 (95%CI 0·47–1·37). Among the control subjects, current smoking was slightly more common among the Leu34-positive women (26%) than the Leu34-negative women (17%), but the distribution of other traditional cardiovascular risk factors (obesity, hypertension, diabetes, hypercholesterolaemia, menopausal status) did not differ according to the presence or absence of the factor XIIIA Leu34 allele (data not shown). There was no association between either the factor XIIIA Tyr204Phe or Pro564Leu polymorphisms and risk of MI (Table II).

Table II. Factor XIIIA genotypes in myocardial infarction (MI) cases, ischaemic stroke cases and controls.

	Controls ($n = 345$)	MI cases ($n = 68$)			Ischaemic stroke cases ($n = 36$)		
	n (%)	n (%)	Model A* OR (95% CI)	Model B† OR (95% CI)	n (%)	Model A* OR (95% CI)	Model B† OR (95% CI)
Val34Leu							
Val/Val	187 (54·2)	41 (60·3)	1	1	16 (44·4)	1	1
Val/Leu	138 (40·0)	24 (35·3)	0·80 (0·46–1·40)	0·81 (0·46–1·42)	14 (38·9)	1·19 (0·56–2·52)	1·27 (0·59–2·72)
Leu/Leu	20 (5·8)	3 (4·4)	0·77 (0·21–2·77)	0·76 (0·21–2·74)	6 (16·7)	3·59 (1·25–10·28)	3·88 (1·33–11·34)
Tyr204Phe							
Tyr/Tyr	324 (93·9)	64 (94·1)	1	1	32 (88·9)	1	1
Tyr/Phe	21 (6·1)	4 (5·9)	1·02 (0·33–3·14)	1·01 (0·32–3·16)	4 (11·1)	1·95 (0·63–6·05)	2·25 (0·70–7·25)
Phe/Phe	0 (0)	0 (0)			0 (0)		
Pro564Leu							
Pro/Pro	218 (63·2)	45 (66·2)	1	1	23 (63·9)	1	1
Pro/Leu	115 (33·3)	20 (29·4)	0·80 (0·45–1·44)	0·80 (0·45–1·44)	12 (33·3)	0·99 (0·47–2·05)	1·04 (0·49–2·20)
Leu/Leu	12 (3·5)	3 (4·4)	1·25 (0·33–4·74)	1·20 (0·32–4·58)	1 (2·8)	0·80 (0·10–6·45)	0·79 (0·10–6·52)

*Model A is adjusted for age only.

†Model B is adjusted for age and the two remaining factor XIIIA polymorphisms.

OR, odds ratio; CI, confidence interval. Reference group for OR is women homozygous for the more common allele (i.e. Val34/Val34 Tyr204/Tyr204 or Pro564/Pro564).

One of our a priori hypotheses was that the decreased risk of MI associated with factor XIIIA Val34Leu may be confined to individuals with other risk factors. Therefore, the risk of MI associated with carrying at least one copy of the factor XIIIA Leu34 allele was stratified according to subgroups defined by traditional cardiovascular risk factors or genetic mutations that have been previously associated with MI risk in this study population (Rosendaal *et al.* 1997a,b; Reiner *et al.* 2001b) (Table III). These data suggest that the decreased risk of MI associated with the Leu34 allele may be confined to subgroups of women with other risk factors (cigarette smoking, obesity, hypertension, menopause or the glycoprotein IIb Ser843 variant). The risk of MI associated with carrying at least one copy of the Leu34 allele was particularly low in the subgroup of women who were obese (age-adjusted OR = 0·33, 95%CI 0·13–0·83). The *P*-value for interaction between factor XIII Val34Leu and obesity was 0·006. The *P*-values for the interactions between factor XIII and the remaining risk factors in Table III were all > 0·05. There was no evidence of interaction between Val34Leu and either the Tyr204Phe and Pro564Leu polymorphisms on the risk of MI (data not shown).

Factor XIIIA polymorphisms and risk of ischaemic stroke

In contrast to the MI cases, the proportion of subjects who carried one or more copies of the Leu34 allele was higher among the ischaemic stroke cases than the control subjects (Table II). There was a particularly high prevalence of the Leu34/Leu34 genotype among women with ischaemic stroke (16·7%) compared with the control subjects (5·8%). This resulted in a nearly fourfold increased risk of ischaemic stroke associated with the Leu34/Leu34 genotype compared with women with the Val34/Val34 genotype. The age-adjusted OR associated with the Leu34/Leu34 genotype compared with women who carried either the Val34/Val34 or Val34/Leu34 genotypes was 3·33 (95%CI 1·23–8·98). The factor XIIIA Tyr204/Phe204 genotype was associated with a ~twofold increased risk of ischaemic stroke, but the confidence interval around this risk estimate was wide owing to the relatively low prevalence of the Phe204 allele.

Table III. Factor XIII Leu34 in myocardial infarction (MI) cases and controls stratified by other environmental and genetic risk factors.

	MI cases (n = 68)		Controls (n = 345)		
Risk factor	V/V	V/L + L/L	V/V	V/L + L/L	OR* (95%CI)
Overall	41	27	187	158	0·80 (0·46–1·40)
Current smoking					
No	12	8	156	117	0·94 (0·37–2·39)
Yes	29	19	31	41	0·49 (0·23–1·05)
Obesity					
No	14	19	138	115	1·68 (0·80–3·51)
Yes	27	8	49	41	0·33 (0·13–0·83)
Hypertension					
No	26	18	173	142	0·86 (0·45–1·65)
Yes	15	9	14	16	0·54 (0·18–1·62)
Diabetes					
No	39	19	182	151	0·61 (0·33–1·10)
Yes	2	8	4	7	2·32 (0·31–17·68)
Hypercholesterolaemia					
No	25	17	155	131	0·84 (0·43–1·64)
Yes	16	10	30	26	0·72 (0·28–1·86)
Menopausal status					
Pre	35	26	180	151	0·90 (0·52–1·57)
Post	6	1	7	7	0·18 (0·01–2·25)
Factor V Leiden or prothrombin G20210A					
Both negative	34	23	173	148	0·80 (0·45–1·43)
Either positive	7	4	12	9	0·87 (0·18–4·10)
Glycoprotein IIb Ser843					
Negative	8	10	74	65	1·43 (0·53–3·87)
Positive	33	17	113	93	0·65 (0·34–1·25)

OR, odds ratio; CI, confidence interval. Data are missing on obesity in two controls, on diabetes in one control, on hypercholesterolaemia in three controls, and on factor V Leiden or prothrombin G20210A in three controls.

*OR and 95% CI calculated for presence of Leu allele (homozygous or heterozygous) compared with Val/Val genotype, and adjusted for age.

Table IV. Co-inheritance of factor XIIIA Phe204 and occurrence of ischaemic stroke in a family with congenital dysfibrinogenaemia.

Heterozygosity for γ-fibrinogen Arg275Cys	Heterozygosity for factor XIIIA Tyr204Phe	Number of family members	Number of family members with ischaemic stroke
–	–	7	0
+	–	4	0
–	+	0	0
+	+	3	2

and compatible with the absence of an association. The distribution of factor XIIIA Pro564Leu genotypes did not differ between ischaemic stroke cases and controls. As with the MI cases, there was no evidence that the risk estimate for stroke associated with any individual factor XIIIA polymorphism was significantly altered by multivariate adjustment for the two remaining polymorphisms (Table II, model B).

We have previously observed an association between risk of ischaemic stroke among these young women and the α_2 integrin C807T polymorphism of the platelet collagen receptor (Reiner *et al*, 2000). When stratified according to genotypes defined by the α_2 integrin C807T polymorphism, all six factor XIIIA Leu34 homozygous ischaemic stroke cases were carriers of the α_2 integrin 807T allele. Thus, the increased risk of ischaemic stroke associated with the factor XIIIA Leu34/Leu34 genotype was present among 807T carriers, but not among women with the 807C/C genotype (P-value for interaction = 0·10).

Factor XIIIA Phe204 co-inheritance and ischaemic stroke in a family with congenital dysfibrinogenaemia

The potential role of the factor XIIIA Ty204Phe polymorphism in occurrence of ischaemic stroke was further supported by genotype analysis of 14 family members from a previously described kindred with congenital dysfibrinogenaemia caused by an Arg275Cys mutation within the gene encoding the fibrinogen γ-chain (Linenberger *et al*, 2000). A man who suffered a fatal ischaemic stroke at age 57 years and his daughter who suffered a non-fatal arterial ischaemic stroke at age 42 years were both doubly heterozygous for the rare γ-fibrinogen Arg275Cys mutation and the common factor XIIIA Phe204 variant. The wife of the man who died of ischaemic stroke at age 57 years was homozygous wild type at both the γ-fibrinogen and factor XIIIA loci. In addition to the affected daughter, the couple had two other children. A 41-year-old son who has suffered recurrent venous thrombo-embolic events also co-inherited the father's γ-fibrinogen Arg275Cys mutation and factor XIIIA Tyr204Phe variant, but has not suffered any arterial thrombotic events while being maintained on therapeutic warfarin since the age of 40 years. A 37-year-old daughter had inherited the father's factor XIIIA Phe204 allele but not the γ-fibrinogen mutation, and was clinically unaffected. The affected father had five siblings (ranging in age from 55 to 64 years), two of whom were heterozygous for the γ-fibrinogen mutation, but none carried the factor XIIIA Phe204 allele. One of the five siblings was a man who was homozygous wild type at both the γ-fibrinogen and factor XIIIA loci, but suffered an acute MI at the age of 60 years in the setting of traditional cardiovascular risk factors (smoking, hypertension) and documented coronary atherosclerosis. The affected father's five siblings had a total of four children (age range 34–45 years); two carried the γ-fibrinogen mutation, none carried the factor XIII Phe204 allele, and all were clinically asymptomatic. Thus, two of three family members who carried both the γ-fibrinogen mutation and the factor XIIIA Phe204 allele had suffered early onset ischaemic stroke, while the third member (who had suffered multiple venous thrombotic events) was chronically treated with warfarin. In contrast, none of the 11 family members who either carried the γ-fibrinogen mutation alone or were homozygous wild type at both loci, have developed ischaemic stroke (Table IV). There was no evidence of a relationship between genotype at either the factor XIIIA Val34Leu or Pro564Leu loci and occurrence of ischaemic stroke among members of this family (data not shown).

DISCUSSION

Our findings from a population-based association study of women under the age of 45 years provide further support for the importance of genetic variation of factor XIII in susceptibility to arterial thrombotic disease. Overall, women who carried at least one copy of the factor XIIIA Leu34 allele had a slightly decreased risk of MI, and the decreased risk was most pronounced among women with other risk factors. Unexpectedly, women who carried two copies of the Leu34 allele had a nearly fourfold increased risk of ischaemic stroke. We also provide evidence that co-inheritance of the factor XIII Phe204 variant may increase the risk of ischaemic stroke among subjects with congenital dysfibrinogenaemia.

A decreased risk of MI associated with the factor XIIIA Leu34 variant has been reported in studies from Great Britain (Kohler *et al*, 1998), Finland (Wartiovaara *et al*, 1999) and Brazil (Franco *et al*, 2000) involving predominantly middle-aged or young men, among whom the reported ORs were in the range of 0·5–0·6. In contrast, other studies involving predominantly men from Southern France (Canavy *et al*, 2000) and Spain (Corral *et al*, 2000) found no association between the factor XIII Leu34 variant and risk of MI. Our data suggest that the inconsistent results

among studies may be related to population differences in the underlying prevalence of other athero-thrombotic risk factors Franco *et al* (2000) also noted that the decreased risk of non-fatal MI among relatively young men and women associated with factor XIIIA Leu34 was most apparent in the presence of traditional cardiovascular risk factors such as hypertension obesity dyslipidaemia and diabetes compared with the absence of these risk factors The British investigators observed that the decreased risk of MI associated with factor XIIIA Val34Leu was only present among patients who did not carry the PAI 1 4G/4G genotype (Kohler *et al* 1998) or did not have features of the insulin resistance syndrome (Kohler *et al* 1999b) Stratification of the risk of MI associated with factor XIIIA Val34Leu according to other risk factors was not performed in the two negative studies from Southern France and Spain (Canavy *et al* 2000 Corral *et al* 2000) Perhaps the decreased risk of MI associated with factor XIIIA Leu34 is clinically non-apparent in Mediterranean populations already protected from arterial thrombotic disease by other mechanisms (Muszbek 2000) Taken together these results suggest that the decreased risk of MI associated with factor XIII Val34Leu is modified by other genetic and environ mental determinants of cardiovascular risk

We also hypothesized that the inconsistent findings among studies that have examined the relationship of Val34Leu with risk of thrombotic disease could arise from partial linkage disequilibrium between Val34Leu and another factor XIIIA polymorphism that is the actual 'causative' mutation This scenario would be particularly likely if the strength of linkage disequilbrium between the two sites varies among different ethnic populations Addi tional factor XIIIA genotype analyses from our study and the study of Kohler *et al* (1999a) provide no evidence that the association between Val34Leu and risk of MI is confounded by linkage disequilibrium with several other known factor XIIIA coding sequence polymorphisms

Our finding of a possible association between Leu34 homozygosity and increased risk of ischaemic stroke at a young age was unexpected and appears to contradict the presumed 'antithrombotic' effect of this genetic variant based on previous studies of MI as well as a recent French study that indicated that carrying at least one copy of the Leu34 allele was associated with a decreased risk of ischaemic stroke (OR = 0 58 95%CI = 0 44–0 75) (Elbaz *et al* 2000) Because of our small sample size owing to the rare occurrence of ischaemic stroke in young women it is possible that our finding represents a chance or spurious result It is unlikely that our results are biased by the exclusion of fatal cases because the case fatality rate for ischaemic stroke in our study population was only 10% Corral *et al* (2000) reported no association between Leu34 and risk of ischaemic stroke but it is interesting to note that the prevalence of the Leu34 allele in their study was higher among stroke cases (42 3%) than among controls (31 7%) Finally the increased risk of ischaemic stroke associated with the Leu34/Leu34 genotype in our study was present only among young women who carried the α_2 integrin 807T allele a prothrombotic genetic susceptibility marker that has been associated with the occurrence of ischaemic stroke at a young age (Carlsson *et al* 1999 Reiner *et al* 2000) This possible gene–gene interaction requires confirmation in larger studies of ischaemic stroke in young adults

The Tyr204Phe polymorphism of factor XIIIA results in reduced factor XIII specific fibrin cross-linking activity and has been associated with increased risk of recurrent miscarriage (Anwar *et al* 1999) Our results suggest a possible association with increased risk of early onset ischaemic stroke which requires confirmation in larger studies We also describe co-inheritance of factor XIIIA Phe204 with a rare fibrinogen γ chain Arg275Cys mutation in two family members who suffered ischaemic stroke and in a third family member with recurrent venous thrombo-embolic disease The fibrinogen γ chain Arg 275Cys mutation results in an abnormal fibrin clot structure and increased clot resistance to fibrinolysis but appears to be associated with clinical thrombo-embolic events only among subjects who carry additional genetic prothrombotic risk factors (Linenberger *et al* 2000 Siebenlist *et al* 2000) A more common fibrinogen Thr312Ala α chain mutation that involves a region important for factor XIII-dependent cross-linking has been associated with venous and arterial thrombo-embolic disease and an interaction has been reported between α fibrinogen Thr312Ala and factor XIII Val34Leu on the risk of pulmonary embolism (Carter *et al* 1999 2000) Taken together these data suggest that factor XIIIA polymorphisms warrant further investigation as possible genetic modifiers of disease susceptibility conferred by other thrombophilic mutations

In conclusion our results suggest that the factor XIIIA Val34Leu polymorphism is associated with decreased risk of MI in young women with other cardiovascular risk factors such as obesity Larger sample sizes will be required to formally test the hypotheses of effect modification with respect to specific genetic lifestyle and metabolic athero thrombotic risk factors Finally the potential role of the factor XIIIA Val34Leu and Tyr204Phe polymorphisms in the occurrence of cerebrovascular disease warrants further mechanistic and epidemiological study of these mutations

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