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Genetic variants of coagulation factor XIII and the risk of myocardial infarction in young women

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Abstract

Introduction Coagulation factor XIII is involved in the crosslinking of fibrin molecules and determines the architecture of the fibrin mesh. Genetic variation in FXIII could lead to differences in clot structure and density. Previous research indicated that genetic variation in genes coding for FXIII increased the risk of ischaemic stroke (IS) nine-fold (204Phe carriers: OR 9.1; 5.5-15). This study aims to determine whether genetic variation in genes coding for FXIII confers a similar increase in risk of myocardial infarction (MI) as with IS.

Methods We determined the four genetic variants in the MI arm (N=218) and control group (N=767) of the RATIO study, a population-based case-control study into risk factors for myocardial infarction and ischaemic stroke in young women (18-50 years). Odds ratios (OR) with 95% confidence intervals were calculated as measures of rate ratios assuming a dominant inheritance pattern.

Results FXIIIA Pro564Leu moderately increased the risk of MI by 40% (564Leu carriers: OR 1.4; 1.0-1.9). This increase in risk was confined to heterozygotes. The other SNPs did not alter MI risk (FXIIIA 34Leu carriers: OR 1.1; 0.8-1.5, FXIIIA 204Phe carriers: OR 0.8; 0.4-1.7 and FXIIIB 95Arg carriers: OR 0.8; 0.5-1.2).

Discussion FXIII SNPs do not play a major role in the aetiology of myocardial infarction whereas they do in IS. This pattern is consistent with earlier results from the RATIO study: prothrombotic defects are important risk factors for IS rather than for MI.

Introduction

Several proteins are involved in thrombus formation. Coagulation factor XIII is, upon activation by thrombin, responsible for the crosslinking of fibrin monomers.[1] The importance of FXIII and its role in haemostasis is demonstrated by the bleeding diathesis of FXIII deficient patients.[2] The protein consists of four chains which are encoded on different chromosomes: two B-chains (encoded on chromosome 1q31 - q32.1) which have no enzymatic activity and serve as carriers of the A-chains, and two A-chains (chromosome 6p25 - p24) that consist of the protransgluteminase which is involved in the crosslinking. This process determines clot structure and clot permeability and resistance to shear stress and fibrinolysis, factors that are of possible importance in pathologic mechanisms underlying thrombotic disease.[3–6] Genetic variants in one of the two genes which encode for coagulation factor XIII (*F13A1* and *F13B*) have been shown to be associated with an altered risk of both arterial and venous thrombosis thrombosis.[7–9] We previously showed that one of these four genetic variants, the *F13A1 204Phe* SNP, was associated with a 9-fold increased risk of ischaemic stroke in young women. Oral contraceptives use further increased this risk (odds ratio 20; 95% confidence interval 9-46).[10]

Since ischaemic stroke (IS) and myocardial infarction (MI) are both manifestations of acute forms of arterial thrombosis, we hypothesised that the risk of MI is also increased by these genetic variants of FXIII. We therefore set out to assess the relationship between these four SNPs in the FXIII genes and the risk of MI in the RATIO study.

Table1. Characteristics of 218 women with a first myocardial infarction and 767 control women.

		Patients N= 218		Control women N=767	
Age	Mean, SD	42.9	6.0	38.6	8.0
Caucasian Ethnicity	N, (%)	207	(95)	723	(94)
History of Hypertension	N, (%)	55	(25)	47	(6)
Diabetes	N, (%)	11	(5)	10	(1)
Hyperlipidaemia	N, (%)	23	(11)	22	(3)
Oral Contraceptive use	N, (%)	86	(39)	272	(36)
Smoking	N, (%)	181	(83)	319	(42)

All variables are measured within respect to the index date for controls and the year of event for cases

Methods

Study design & participants The Risk of Arterial Thrombosis In relation to Oral contraceptives (RATIO) study is a multicenter, population-based case-control study. The study consists of 3 arms, on MI, IS and peripheral arterial disease, of which details have been published earlier.[11–13] In short, for this study we included 218 women aged 18 to 50 years who were hospitalised for a confirmed first MI in one of 16 participating hospitals. Random digit dialling yielded 767 women aged 18 to 50 years who served as controls; the control group was frequency-matched to the patients for age (in five-year categories), residence, and index year. Furthermore, the women did not have a history of coronary heart disease, cerebrovascular event, or peripheral vascular disease. All participants filled in a questionnaire on possible risk factors and medical history focused on cardiovascular. diseases and provided DNA. Informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Measurements A total of 4 genetic variants was genotyped with the 5' nuclease/TaqMan assay: Val34Leu (rs5985), Tyr204Phe (rs3024477), and Pro564Leu (rs5982) variants in the FXIII subunit A gene (*F13A1*) and the His95Arg variant (rs6003) in the FXIII subunit B gene (*F13B*). Primer sequences, probe sequences, and restriction enzymes used are available on request. Laboratory technicians were unaware of case-control status and other patient characteristics.

Statistical Analysis The effect of the genetic variation in the genes encoding for FXIII on the risk of MI was assessed by the calculation of odds ratios as measures of rate ratios with the corresponding 95% confidence intervals with logistic regression. Odds ratios were calculated per genotype and according to dominant inheritance pattern and were adjusted for the stratification factors age (on a continuous scale), area of residence and index year.

Results

The baseline characteristics of patients and controls are displayed in table 1. As expected, patients reported more cardiovascular risk factors than controls. Genotype distributions and corresponding odds ratios are shown in table 2. The overall call rate was 97.8% (range, 96.1% - 98.7%). No deviation from Hardy-Weinberg equilibrium was found in the control women for any of the genotypes. Only the *F13A1* 564Leu variant of the *F13A1* gene was associated with an increased risk of 40% (OR 1.40; 95% confidence interval 1.01 – 1.93) in the dominant inheritance pattern analysis. The increase in risk for the *F13A1* Pro564Leu

Table 2. Genotype distribution amongst cases and controls and their corresponding risks for myocardial infarction

Gene variant		Allele frequency	Myocardial infarction patients N=218			Control women N=767			Odds Ratio	
			AA	AB	BB	AA	AB	BB	OR	95% CI
F13 A1	Val34Leu (rs5985)	0.25	124 (57)	80 (37)	14 (6)	419 (56)	283 (38)	45 (6)	1.07	0.78 - 1.48
F13 A1	Tyr204Phe (rs3024477)	0.03	208 (95)	10 (5)	0 (0)	711 (94)	42 (6)	1 (0)	0.82	0.39 - 1.71
F13 A1	Pro564Leu (rs5982)	0.21	119 (55)	91 (42)	7 (3)	466 (62)	251 (33)	34 (5)	1.40	1.01 - 1.93
F13 B	His95Arg (rs6003)	0.09	185 (86)	28 (13)	3 (1)	609 (83)	112 (15)	9 (1)	0.79	0.50 - 1.24

AA = major allele homozygote (non-carrier), AB = heterozygote (carrier), BB = minor allele homozygote (carrier). Allele frequency in control population. Odds ratios are calculated for carriers of the gene variant (i.e. dominant inheritance pattern is assumed) and are adjusted for the stratification factors age, calendar year of the index event, and area of residence.

variant was confined to the heterozygous carriers (1.46; 1.05 – 2.03): the homozygous carriers of the minor allele had the same risk of disease as the homozygous carriers of the major allele (0.96; 0.40 - 2.28). The variants *F13A1* Val34Leu, *F13A1* Tyr204Phe and *F13B* His95Arg SNPs did not affect the risk of MI in both the dominant and the per genotype analyses.

Discussion

The *F13A1*564Leu variant is the only variant that affected the risk of MI in our study. This SNP has been associated with both a lower FXIII plasma level and an increase FXIII activity.[14,15] This, together with the lack of dose response, does not add to a plausible biologic mechanism which explains the increase in risk of MI in heterozygotes, nor does the absence of an effect in homozygotes. This suggests that the minor increase in risk we observed for the heterozygous genotype is a false positive finding.

An earlier study on FXIII SNPs suggested an increase risk of IS for *F13A1* 34Leu and *F13A1* 204Phe, but not for MI.[7] However, due to the limited number of cases (68 MI cases and 36 IS cases) no definite conclusions could be drawn. The modest protective effect of *F13A1* 34Leu variant on MI could not be replicated, probably due to lack of power.[8] Earlier results from the RATIO study showed a nine-fold increased risk of ischaemic stroke for carriers of the *F13A1* 204Phe whereas carriers of the *F13B* 95Arg variant had a 1.7 fold increase in the risk of myocardial infarction.[10]

Conclusion Although myocardial infarction and ischaemic stroke are both acute manifestations of arterial thrombosis, SNPs in the FXIII genes have different effects. Even

though the exact underlying causal mechanism cannot be established from these data, these differences in effects suggest that FXIII has a different role in the aetiology of MI and IS. Further study into the differences between the aetiology of myocardial infarction and ischaemic stroke is warranted.

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