Factor V Leiden in Chioggia: a prevalence study in patients with venous thrombosis, their blood relatives and the general population

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Introduction

Factor V Leiden (FVL) is the most common genetic polymorphism known to predispose to episodes of venous thromboembolism (VTE) in western countries; heterozygosity for FVL occurs in 3-8%, and the rate of homozygosity is around 1/5,000 in the general population in Italy[1]. As previously reported, we observed a very high prevalence of FVL carriers in patients with deep venous thrombosis in Chioggia. Among 292 consecutive patients attending our Laboratory for investigation of thrombophilic risk factors after an episode of venous thrombosis we observed 168 (57.5%) normal subjects and 124 (42.5%) FVL carriers: 13 (4.5%) of whom were homozygous for the polymorphism and 111 (38.0%) heterozygous[2,3].

The high prevalence of FVL carriers among patients with venous thrombosis should be due to case selection but may also reflect a high diffusion of this particular mutation in Chioggia. The aim of this study was to establish the correct prevalence of FVL carriers in our area by evaluating patients, their blood relatives and the general population.

Materials and methods

Selection of subjects

We evaluated 934 subjects divided into four groups. Group A (n=229) consisted of patients studied after a venous thrombosis; these patients were aged from 19 to 78 years (mean 63.4 years), 146 (64%) were females and 82 (36%) were males. Group B (n=234) was formed of blood relatives of the patients enrolled in group A; these relatives were aged from 18 to 71 years (mean 58.3 years), 128 (55%) were females and 106 (45%) were males. Group C (n=231) consisted of women evaluated before prescription of birth control pills; these women were aged between 17 and 43 years (mean 31.7 years). Group D (n=240) comprised male, repeat blood donors enrolled in our transfusion service; these men were aged from 18 to 65 years (mean 45.4 years).

Laboratory tests

In our Laboratory the first line approach to the diagnosis of FVL diagnosis is based on functional tests. Activated C protein resistance is detected using a Sysmex CA 7000 analyser and a prothrombin-based assay (Pefakit APC-R, Pentapharm Ltd., Basel, Switzerland).

For genetic tests we adopted a commercial automated analyser, LightCycler, with software version 3.5, and the commercially available Factor V Leiden Kit for the detection of the FVL G1691A mutation. The analyser and assay methods were supplied by Roche S.p.A., Milan, Italy.

Statistical analysis

The statistical analyses were conducted using dedicated software: Analyse.it version 2.03 (Analyse.it Software Ltd., Leeds UK). The χ^2 test was used for comparison of proportions and p values less than 0.05 were considered statistically significant.

Results

Among the 934 subjects considered we detected 214 FVL carriers giving an overall prevalence of 22.9%: 197 (21.1%) of the subjects were heterozygous for the polymorphism and 17 (1.8%) were homozygous.

Among the 229 patients with previous venous thrombosis we found 131 (57.2%) normal subjects and 98 (42.8%) FVL carriers: 88 (38.4%)

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heterozygous and 11 (4.8%) homozygous. Among the 234 blood relatives of patients with previous venous thrombosis we observed 175 (79.8%) normal subjects and 59 (25.2%) FVL carriers: 55 (23.5%) heterozygous and 4 (1.7%) homozygous. Among the 231 women evaluated before prescription of birth control pills we found 201 (87.1%) normal subjects and 30 (13.1%) FVL carriers: 29 (12.6%) heterozygous and 1 (0.4%) homozygous, whereas among the 240 repeat male blood donors we found 214 (89.2%) normal subjects and 26 (10.8%) FVL carriers: 25 (10.4%) heterozygous and 1 (0.4%) homozygous. These data are presented in Table I.

Statistical analysis showed a significantly higher prevalence of FVL carriers in group A compared to group B ($p<0.001$) and groups C and D ($p<0.0001$). The prevalence of FVL carriers was also higher in group B than in groups C and D ($p<0.005$).

Table I - Prevalence of factor V Leiden carriers in the considered cohorts of subjects

Group	Subjects	Normal		Heterozygous		Homozygous	
		N.	%	N.	%	N.	%
A	229	129	56.3	88	38.9	11	4.8
B	234	175	79.8	55	23.5	4	1.7
C	231	201	87.1	29	12.6	1	0.4
D	240	214	89.2	25	10.4	1	0.4

Group A: 229 subjects studied after a venous thrombosis
Group B: 234 blood relatives of the patients enrolled in group A
Group C: 231 women before prescription of oral contraception
Group D: 240 repeat male blood donors

Discussion

Chioggia is a town of about 60,000 inhabitants built in a group of islands in the southern part of the Venetian lagoon and, until 50 years ago, it was particularly secluded. As a consequence three family names (Boscolo, Tiozzo and Penzo) account for about 50% of the names of the whole population. The annual incidence of venous thrombosis observed in our area is around one case each 1,000 subjects[4], with this finding being in good agreement although slightly higher in comparison with results published by other authors[5,6]. We previously reported a high prevalence of FVL carriers in patients evaluated in our Laboratory to investigate thrombophilic risk factors after an episode of venous thrombosis[2-4]. In this study we evaluated the prevalence of FVL carriership in four cohorts of subjects: apparently healthy individuals from the general population (represented by male blood donors and women before prescription of birth control pills), patients who had had previous venous thrombosis and their blood relatives. All these individuals had local ancestry and were selected on the basis of the above reported family names. In this study we evaluated 229 patients with previous thrombosis (group A), 234 of their blood relatives (group B), 231 women before prescription of birth control pills (group C), and 240 repeat male blood donors (group D).

The data obtained in this study confirmed the high prevalence of FVL carriers in our area. The prevalence of FVL carriers in group A was 42.8%, with 4.8% of the subjects being homozygous for the polymorphism; this prevalence is higher than that reported by other authors in similar series[1,5,6].

We considered the subjects in groups C and D as representative of the unselected, general population. In these groups the overall prevalence of FVL carriers was 11.9% higher than data reported in literature for the general Italian population[1,7 8].

The results observed in group B are of particular interest. In this group, consisting of patients' blood relatives, we observed a prevalence of FVL carriers (25.2%) that was intermediate between the prevalence in patients and the general population. These data indicate, on a background characterised by a high prevalence of FVL carriers also in the general population, the presence of a group of families – comprising patients with venous thrombosis and their blood relatives - in which FVL carriers are particularly frequent. Our data suggest that in these families the presence of FVL is a risk factor for the development of thrombosis. It should, however, be noted that the subjects in group A were older than those in group B and age is a very important thrombophilic risk factor. Moreover, in this study we did not investigate concomitant clinical conditions, such as cancer, surgery and immobilisation[9,10]. A randomised, prospective study is needed to assess the importance of FVL as a thrombophilic risk factor in Chioggia.

In conclusion, the results of this study confirmed the high prevalence of FVL carriers in Chioggia not

only in patients with previous thrombosis but also in healthy individuals from the general population and blood donors.

Key Words: FVL, thrombosis, risk factor, general population, family study.

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