High Prevalence of Factor V Leiden Mutation is Detected in a North to South Axis through Germany

Eine hohe Prävalenz der Faktor V Leiden Mutation verläuft in einer Nord-Südachse durch Deutschland

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Abstract: The most common inherited thrombophilic diathesis is activated protein C (APC) resistance, caused by the factor V (FV)-Leiden mutation. The aim of the present study was to obtain reliable data on the prevalence of this disorder in Germany. Therefore, a large number of DNA specimens from different areas was investigated by restriction fragment length polymorphism analysis. In total, 3130 erythrocyte concentrate specimens from blood donors and 835 blood samples from non-selected subjects were evaluated. A mean prevalence of 5.9% of the FV Leiden mutation was found in German blood donors, which is between the values reported for the general population in Sweden and The Netherlands. The highest prevalence was detected in Würzburg and Göttingen (7.3% each), the lowest in Dresden (3.0%). Freiburg, Homburg/Saar, Hamburg, and Bonn revealed intermediate values (6.4%, 5.9%, 5.8%, and 5.2%, respectively). Comparing blood donors to the general population, approximately 1% higher prevalence in the latter could be observed. The present data demonstrate a high prevalence of the FV Leiden mutation in Germany. They indicate a regionally unequal distribution of this predisposition for venous thromboembolism. Combination of the present data with prevalence data already reported for Germany and European neighbour states, drawn into a map, demonstrated high prevalence in an axis from the north to the south, decreasing to the east as well as to the west.

Keywords: Alleles; Europe; Factor V/genetics; Genetics, Population; Gene Frequency; Germany; Mutation; Thromboembolism/genetics.

Zusammenfassung: Die APC Resistenz, verursacht durch die FV Leiden Mutation, stellt die häufigste hereditäre thrombophile Diathese dar. Ziel der hier vorgestellten Untersuchungen war es, zuverlässige Daten über die Prävalenz dieser Mutation in Deutschland zu erhalten. Hierzu wurde eine große Zahl von DNS-Proben aus verschiedenen Gebieten Deutschlands durch Analyse des Restriktions-Fragment-Längen-Polymorphismus untersucht. Insgesamt konnten 3130 Erythrozytenkonzentrate von Blutspendern und 835 Blutproben von unselektionierten Probanden untersucht werden. Es zeigte sich, daß die FV Leiden Prävalenz in Deutschland sehr hoch ist und bei Blutspendern mit einem Durchschnittswert von 5,9% zwischen den Werten liegt, die für die allgemeine Bevölkerung in Schweden und den Niederlanden berichtet werden. Höchste Prävalenzwerte wurden in Würzburg und Göttingen gefunden (jeweils 7,3%), der niedrigste Wert wurde für Dresden bestimmt (3.0%). Freiburg, Homburg/Saar, Hamburg und Bonn ergaben dazwischen liegend Werte (6,4%, 5,9%, 5,8% bzw. 5,2%). Ein Vergleich von Blutspendern zur Normalpopulation zeigte, daß in der letztgenannten Population die Prävalenz um ca. 1% höher lag. Die vorgestellten Daten zeigen eine hohe Prävalenz der FV Leiden Mutation in Deutschland und deuten auf eine regional unterschiedliche Verteilung hin. Durch Zusammenführen dieser Daten mit anderen verfügbaren Prävalenzdaten aus anderen Gebieten Deutschlands sowie aus europäischen Nachbarstaaten zeigt sich in einer hierzu erstellten Landkarte eine Achse hoher Prävalenzen, die von Nord nach Süd verläuft und einen Abfall der Prävalenzen für diese Mutation nach Ost und West.

Schlüsselwörter: Allele; Deutschland; Europa; Faktor V/Genetik; Genetik, Populations-; Genhäufigkeit; Mutation; Thromboembolie/Genetik.

Thromboembolic events are major clinical complications that can even lead to life-threatening situations. The most common inherited risk factor for venous thromboembolism is the APC resistance [1]. The hypercoagulable state in APC resistance is indicated by elevated levels of F1+2 and thrombin-antithrombin III-complex [2, 3]. Besides being inherited, APC resistance can also be acquired, influenced by various parameters such as age, sex [4], and intake of oral contraceptives [5, 6]. More than 90% of the inherited APC resistance is caused by an amino acid exchange (R → Q) in the coagulation factor V (FV) at position 506. The underlying mutation in the FV gene (base transiti-

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Received: April 28, 1997

on G → A at position 1691: "FV Leiden" [7], seems to be common in Western Europe and in people with their origin in Western Europe [8], but appears to be rare in Asia [9] (e.g. China <0.2%) and amongst Negroid and Inuit populations [10, 11].

Compared to healthy people, the risk for a thromboembolic event is 5-10 times increased in heterozygotes, in homozygotes even 80 times [12]. Of all thromboembolitic events 16-60% are associated to FV Leiden [13], and this mutation is thought to cause up to 46% of the observed thromboembolic events in pregnancy [14]. The clinical relevance of FV Leiden is thus more than obvious.

Preliminary studies [15] and data from other investigators [8, 16, 17] revealed that FV Leiden is not equally distributed, thus raising the question whether the same might also be true for smaller areas.

In the present study, we investigated the distribution of FV Leiden in different areas of Germany in order to assess the regional distribution and to obtain reliable data on the general prevalence of this mutation.

Material and methods

Sample preparation: DNA was purified from EDTA blood or from erythrocyte concentrate specimens (taken from tube segments of blood bags) using the QIAAmp technique (Qiagen, Hilden, Germany) according to the manufacturers' instructions. Briefly after proteolytic digestion of 200 µl erythrocyte concentrate, the containing DNA was bound to ion exchange columns under chaotropic conditions. Following a washing step, DNA was eluted in 100 µl Tris buffer (20 mmol/l Tris, pH 8.0). High number of samples could be handled by the use of the QIAAmp 96 blood kit (Qiagen) which allows the simultaneous preparation of up to 192 samples. Polymerase chain reaction [18] (PCR) of FV was performed according to *Bertina* et al. [7] with some minor modifications. Briefly primers (MWG-Biotech, Ebersberg, Germany) were applied in a touch down PCR, decreasing the annealing temperature from initially 65 °C to 55 °C within 10 cycles, followed by 30 cycles PCR (annealing, extension, and denaturation temperature, 55 °C, 65 °C and 95 °C respectively, 1 min each (Thermocycler, TC 1, Applied Biosystems, Weiterstadt, Germany). In a total volume of 30 µl, aliquots of the PCR products were digested with restriction enzyme Mnl I (100 U/ml, Biolabs, Schwalbach, Germany; recognition site CCTC(N)7/6) in appropriate buffer conditions for 10 h at 37 °C. Restriction fragment length polymorphism (RFLP) was analysed using a mini gel chamber (Pharmacia, Freiburg, Germany) and a low melting point (LMP) agarose gel system (1X TBE, 2% LMP; Sigma, Deisenhofen, Germany). DNA fragments were stained for 10 min in ethidiumbromide (25 mmol, Sigma) in 1X TBE) and made visible by UV light radiation. The presence of G1691A mutation was confirmed by a second amplification and restriction-enzyme digestion.

Statistical analysis was performed using the SPSS software package (SPSS GmbH, Munich, Germany). Differences between two areas were considered to be statistically different when $P<0.05$ applying the χ^2-test. If necessary Fisher T test ($P<0.05$) was applied additionally.

Results

In the present study DNA from erythrocyte concentrate specimens of 3130 German blood donors derived from Bonn, Dresden, Freiburg, Göttingen, Hamburg, Homburg/Saar, and Würzburg were analysed for the presence of the FV Leiden mutation (table 1). Furthermore, DNA of volunteers from Würzburg (non-selected gynaecological patients, n=406) and from Deggendorf (n=429) was investigated (see table 1).

After RFLP 6260 alleles of German blood donors could be analysed for FV Leiden mutation (table 1). The loss of the Mnl I recognition site caused by the transition of G → A at position 1691 (FV Leiden) was found on 191 alleles (3.1%). The prevalence of the FV Leiden mutation in German blood donors is thus as high as 5.9%. This value was found to be significantly lower than the prevalence calculated for the normal population (7.3%) (table 1).

Distinguishing between single regions, differences in the prevalence values even within a small country like Germany became obvious. The highest values were obtained for Würzburg and Göttingen (7.3%, n=496 and n=532, respectively), followed by Freiburg (6.4%, n=409), Homburg/Saar (5.9%, n=337), and Hamburg (5.8%, n=416). In contrast, Bonn and Dresden revealed a low prevalence (5.2%, n=610 and 3.0%, n=330, respectively). Significant differences could be found while comparing areas with high prevalence to ones with of low prevalence for the FV Leiden mutation: see table 1 for details.

Furthermore, a total of 1670 FV alleles from blood samples of volunteers (Deggendorf, n=429; Würzburg, non selected gynaecological patients, n=406) were analysed. The prevalences within these populations were found to be 8.1% and 8.4%, respectively. These values were found to be significantly higher than the prevalence found in other regions and also significantly different to the mean values calculated for German blood donors and German general population (see table 1). Thus these data demonstrate for the first time a significant unequal distribution of the FV Leiden mutation in Germany.

Comparing blood donors from Würzburg to non-selected gynaecological patients an increase of the FV Leiden prevalence from 7.3% to 8.9% was observed.

Non-standard abbreviations: APC, activated protein C, APTT, activated partial thromboplastin time; F1+2, (prothrombin) fragment 1 + 2; FV, factor V; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

The impression of a obviously selection towards haematologically healthy people in the blood donor group was strengthened by the observation of a statistical difference, when comparing the mean values calculated for German general population and German blood donors (7.3% and 5.9% respectively, table 1).

Comparing the values obtained for the German general population to those reported for neighbour states, further differences became obvious. The mean prevalence calculated for the German general population was significantly higher than the prevalences reported for neighbour states in the west, like The Netherlands and France, states in the south like Switzerland and Italy and in the east being statistically higher than Slovenia and Bohemia (see table 2). This again demonstrates a unequal distribution of this mutation and a concentration of an area of high prevalence for FV Leiden mutation in an axis from north to south running through Germany.

Discussion

FV Leiden is by far the most common risk factor for venous thromboembolism, at least in Western Europe. The incidence of the mutation lies between 16% and 60% in the thrombophilic patients [13, 19]. Certainly, a number of thromboembolitic events would be prevented, if thrombophilic individuals knew about their additional risk and could therefore take precautions, at least in risk situations. In this context, reliable data are needed that allow estimation of the general risk within a certain population.

Compared to neighbour states (table 2), the overall prevalence of FV Leiden of 5.9% amongst German blood donors (table 1) is very high. In selected healthy people like blood donors (especially from the point of view of haemostatic disorders) a higher prevalence has not yet been reported. The prevalence within an non-selected population should be assumed to be even higher! Indeed the value increased from 7.3% (blood donors from Würzburg) to 8.9%, when non-selected gynaecological patients were investigated (table 1). As the latter exclusively consists of women, one might -at first sight- expect an unequal distribution between sexes. However, this is only true for acquired APC resistance [6, 20], and *not* true for the FV Leiden mutation [16, 21].

Due to previous and present data, a regional unequal distribution of the FV mutation can be assumed. This hypothesis is supported by observations of other research groups from Germany and from neighbour states (tables 1 and 2). Low values were reported from France [22, 23], Italy [20, 24] and amongst the Slovenian [25] and the Czech-Bohemian [26] population. Unfortunately, most of these data were obtained by functional protein analysis (APTT based APC resistance test systems) and are thus not directly compar-

Table 1 Prevalence of FV Leiden mutation in different areas of Germany according to DNA analysis

No	sample origin [reference]	number of samples	genotype GG	AG	AA	prevalence of FV Leiden (%)	different to No*
1	Würzburg[1]	496	460	35	1	7.3	8, 9
2	Göttingen[1]	532	493	38	1	7.3	8, 9
3	Freiburg[1]	409	383	26	0	6.4	8
4	Homburg/Saar[1]	337	317	20	0	5.9	8, 19
5	Hamburg[1]	416	392	23	1	5.8	8, 12, 19
6	Bonn[1]	610	578	32	0	5.2	1, 2, 10, 12, 14, 19
7	Jena[1] [36]	103	99	4	0	3.9	1, 2, 3, 5, 9, 10, 12, 13, 14, 19
8	Dresden[1]	330	320	9	1	3.0	1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 14, 15, 17, 19
9	total blood donors	3233	3042	187	4	5.9	8, 12, 19
10	Würzburg[3]	406	370	31	5	8.9	5, 6, 8, 9, 18, 19
11	Kiel [37]	117	107	10	0	8.5	5, 6, 8, 9, 18, 19
12	Deggendorf[2]	429	394	32	3	8.2	6, 8, 9, 18
13	München [38]	180	166	14	0	7.8	6, 8, 9
14	Greifswald [17]	814	756	56	2	7.1	8, 9
15	Kaiserslautern [39]	204	190	14	0	6.9	8, 9
16	Hannover [40]	108	101	7	0	6.5	8
17	Münster [41]	222	208	14	0	6.0	8
18	Freiburg [42]	196	188	8	0	4.1	1, 2, 3, 9, 10, 11, 12, 13, 14,15, 19
19	total general population	2676	2480	186	10	7.3	6, 8, 9

* χ^2 Test: $P<0.05$, if necessary, additionally Fisher T test $P<0.05$
[1] blood donors; [2] unselected volunteers; [3] Non-selected gynaecological patients

able to a DNA-based analysis. However, since APTT based test systems give rather false positive results (own unpublished observation) [27, 28] in these cases the FV Leiden prevalence has to be considered being even lower, thus building an even steeper gradient. Reports from Great Britain [29], The Netherlands [12], Austria [30], and Poland [16] are directly comparable to the present data as they are also based on DNA analysis. As demonstrated in figure 2 and table 2 statistically significant differences between European countries became obvious.

Taking the data from table 1, the area of high FV mutation forms a north to south axis from Kiel/Greifswald via Göttingen and Würzburg to München, with a significant decrease of the prevalence in the neighbour states (table 2) in the south east and the west (table 1 and 2, figure 1 and 2). A decrease to the south is observed with respect to the data reported from Switzerland and Italy (table 2, figure 2). This remarkable distribution pattern continues also in France, where the highest prevalence is reported for the north eastern area (close to the German border) and low values are reported for the south and for the west [22, 23] (table 2).

The observation of an unequal distribution of FV Leiden mutation in Europe raises several questions regarding the origin and the selection pressure on the mutation. In pregnancy, a slight hypercoagulable state, indicated by a decreased APC ratio [31], can be observed. This physiological feature can be intensified by the FV mutation. Thus, a positive selection pressure on FV Leiden mutation could eventually be related to early events in embryonic development [32].

The thesis of *Fujimura* and coworkers [33] that FV Leiden mutation is subject to a specific selection pressure due to racial background cannot be supported by the present study, as even among the German population significant differences in the prevalence could be demonstrated. The unequal distribution even in a small country like Germany further raises the question whether a positive selection pressure on this mutation was ever present and if so - if it eventually would still be active. A strong accumulation in restricted areas could point towards a so-called "founder effect" in which a single mutation event at this hot spot for mutation, namely at bases CpG [35], originates in central Europe. From here the mutation seems to spread to other populations. Moreover, taking the "founder effect" as a fact, it could be assumed -due to the present results- that the mutation is perhaps much younger than 100,000 years, as estimated by *Cox* [35].

More extensive genetic analysis of the distribution of FV Leiden in Europe, as well as in other populations, will certainly help to elucidate the mentioned

Table 2 Prevalence of FV Leiden mutation in Germany and neighbour states

No	sample origin	[reference]	number of samples	genotype GG	genotype AG	genotype AA	prevalence of FV Leiden (%)	method	different to No*
1	Germany general population		2676	2480	186	10	7.3	DNA	4, 5, 6, 7, 10
2	Sweden	[21]	130	121	9		6.9	APC-R	1, 7, 8, 9
3	Great Britain	[29]	144	139	5		3.5	DNA	1, 7, 8, 9
4	Netherlands	[12]	474	460	14		3.0	DNA	1, 7, 9
	France	[22]	300	292	8		2.7	APC-R	
			193	176	16	1	8.8	DNA	
		[23]	148	147	1	0	0.6	DNA	
			207	201	6	0	2.9	DNA	
5	total France		848	816	32		3.8		1, 7, 9
	Switzerland	[43]	348	334	14		4.0	APC-R	
		[44]	234	229	5		2.1	APC-R	
6	total Switzerland		582	563	19		3.3	APC-R	1, 7, 9
	Italy	[20]	1628	1605	23		1.5	APC-R	
		[24]	344	335	9		2.6	DNA	
7	total Italy		1972	1940	32		1.6		1, 2, 4, 5, 6, 9, 10, 11,
8	Slovenia	[25]	100	97	3	0	3.0	APC-R	1, 7
9	Austria	[30]	107	96	11	0	10.3	DNA	1, 2, 3, 4, 5, 6, 7, 8, 10, 11
10	Bohemia	[26]	400	386	14		3.5	APC-R	1, 7, 9
11	Poland	[16]	200	190	10	0	5.0	DNA	1, 4, 7, 9

*: χ^2 Test: $P<0.05$, if necessary, additional Fisher T test $P<0.05$

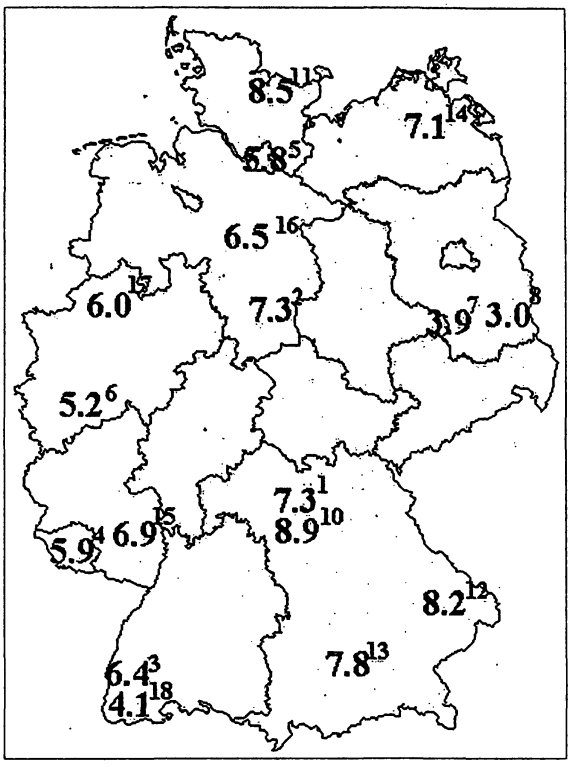

Figure 1 Prevalence of FV Leiden: unequal distribution in Germany. Relative frequencies (%) and references to the group numbers in table 1 are shown

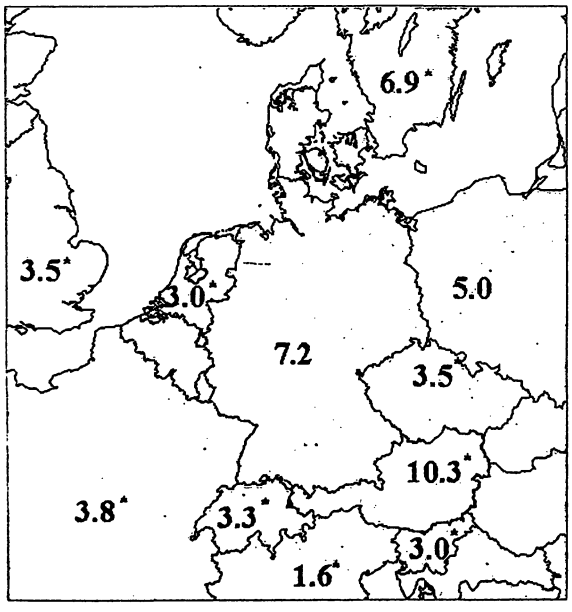

Figure 2 Prevalence of FV Leiden: unequal distribution in Europe. Relative frequencies (%) are shown.
* statistically different to Germany (see table 2)

questions. As commercially available tests for APC resistance can certainly help to detect defects within the protein C system but are not reliable for screening of FV Leiden mutation [27, 28], DNA analysis is an essential prerequisite.

Based on the high prevalence of the FV Leiden mutation in the general German population, more than 30,000 thromboembolic events per year can be connected to this genotype. The awareness of a very high prevalence of FV Leiden in certain areas could certainly help to sensitize physicians for the necessity of screening for this mutation, especially in groups carrying additional risk factors (such as immobilization, surgery, intake of oral contraceptives). Informed carriers will be able to recognize and avoid risk situations, with the consequence that a number of thromboembolic events might be prevented.

Acknowledgement: Dr. *Beck,* Universität Freiburg; Dr. *Hölig,* Dresden; Dr. *Huber* Deggendorf; Dr. *Lubitz,* Hamburg; Dr. *Oldenburg,* Bonn; Dr. *Seyfart,* Universitätsklinik Homburg/Saar; and Dr. *Wieding,* Universitätsklinik Göttingen are gratefully acknowledged for blood donor sample collection. Dres. *Spengler, Schwab, Scheuer* and *Schmitt* are acknowledged for collecting samples from gynaecological patients. Mrs. *P. Hochrein* is expressly thanked for invaluable technical assistance of this project. Mrs. *Misoph* is gratefully acknowledged for reviewing the manuscript.

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Industriemitteilung

Rolf G. Heller ist neues Mitglied der Geschäftsleitung der Bayer Diagnostics GmbH München

Zum 1. April 1997 ist Rolf G. Heller in die Geschäftsleitung der Bayer Diagnostics GmbH, München, eingetreten. Herr Heller übernimmt damit die Geschäftsbereichsleitung des Diagnostika-Geschäfts des Bayer Konzerns in Deutschland. Zu seinem Verantwortungsbereich gehört auch das Bayer Diagnostika-Geschäft in Österreich. Er ist Mitglied des Führungsteams der Bayer Vital GmbH & CoKG.

Herr Heller kommt zu Bayer Diagnostics mit über 25 Jahren DuPont und Dade International Erfahrung. Dabei war er in Managementpositionen in Italien, Skandinavien, Deutschland und Osteuropa tätig. Dem Gesundheitswesen ist er seit 1983 über die Bereiche Diagnostische Bildverfahren (Röntgen) sowie Diagnostika und Biotechnologische Systeme verbunden. Nach dem Verkauf des Geschäftsbereichs Medizinische Produkte der Firma DuPont wechselte er mit dem Diagnostika-Geschäft zur Firma Dade International. Herr Heller wurde Geschäftsführer der neuen VDGH (Verband der Diagnostica-Industrie e.V.). Im Februar 1997 wurde Herr Heller für weitere zwei Jahre gewählt.

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