Leids Universitair Medisch Centrum

Factor V Leiden en het voorkomen van trombose in families

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Inhoud

- Bloedstolling: pro- en anticoagulante factoren in het bloed
- Erfelijke risicofactoren voor trombose
- Ontdekking van factor V Leiden

Waarschuwing

- ‘Uit de oude doos’
- Inspanningen van een grote groep onderzoekers
- Niet iedereen wordt genoemd
- Paradox: ontdekken is ‘fun’ maar trombose is helemaal niet funny
- Ik ben geen arts en klinische vragen kan ik moeilijk beantwoorden

Leidse ontdekkingen

leidendiscoveries.nl

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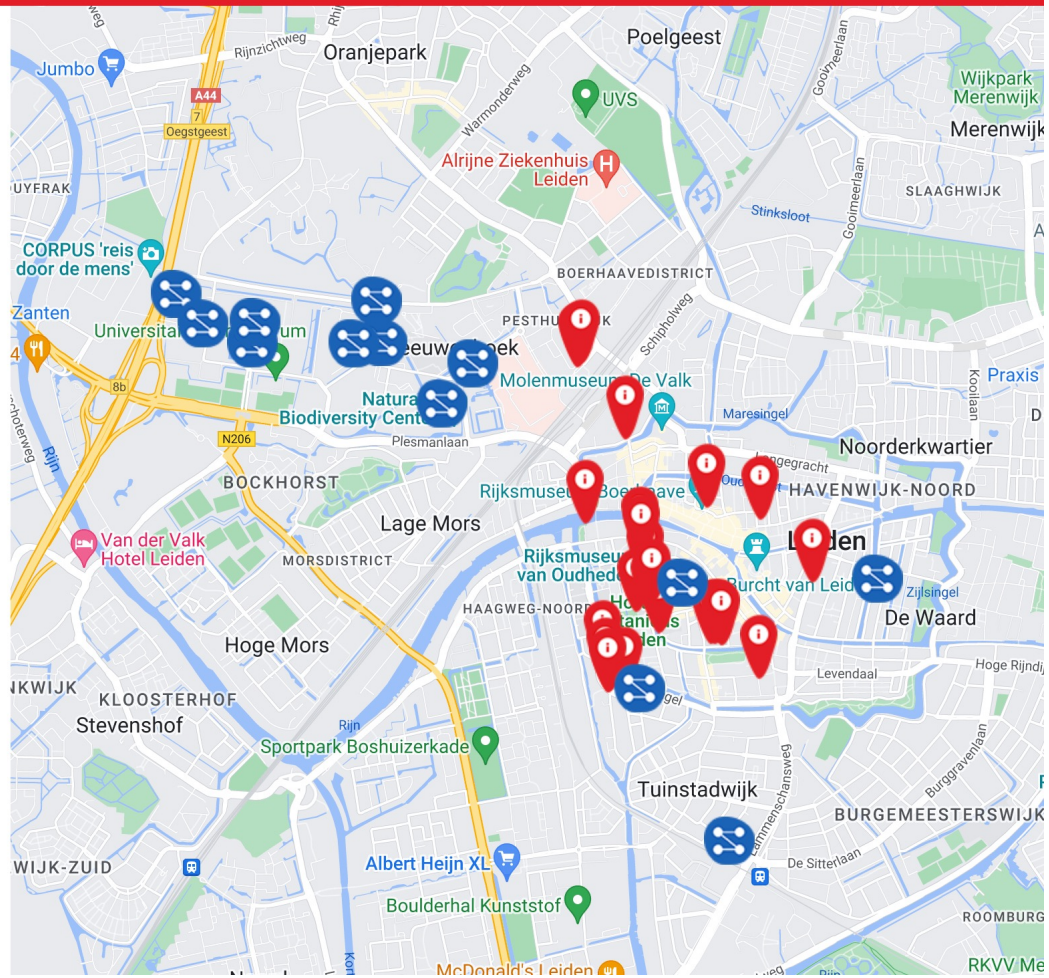
› Home › Route › Ontdekkingen › Applicatie › De stichting › Partners English ›

Ontdekkingen

- Elektrocardiograaf
- Diergedrag
- Supergeleiding
- Tulpencultuur
- Grondwet
- Galileo's Discorsi
- Leidsche Fles, Condensator
- Breking van het licht
- Japanse cultuur
- Eerste leerstoel archeologie in de wereld
- Eerste heelal-model volgens de relativiteitstheorie
- Structuur van de Melkweg
- Radiosterrenkunde
- Tiendelige breuk
- Elektronentheorie
- Immuunsysteem en orgaantransplantatie
- Factor V Leiden
- Middeleeuwen
- Econometrie
- Elektronenspin
- Uitzetting materie bij verwarming; (1/2)mv^2
- Ploem Fluorescentiemicroscoop
- Antropologie der primitieve kunst, etnocinematografie
- Adat-recht
- Moleculaire thermodynamica
- De herkomst van kometen
- Sylvius •
- Ehrenfest Theorema •
- Shubnikov-De Haas effect & De Haas-van Alphen effect •
- Kramers-Wannier dualiteit •
- Katwijkse Ziekte •
- Oosterhoff-Havinga Regels •
- Z-DNA •
- Detectie van baarmoederhalskanker •
- De eerste 35 decimalen van pi •



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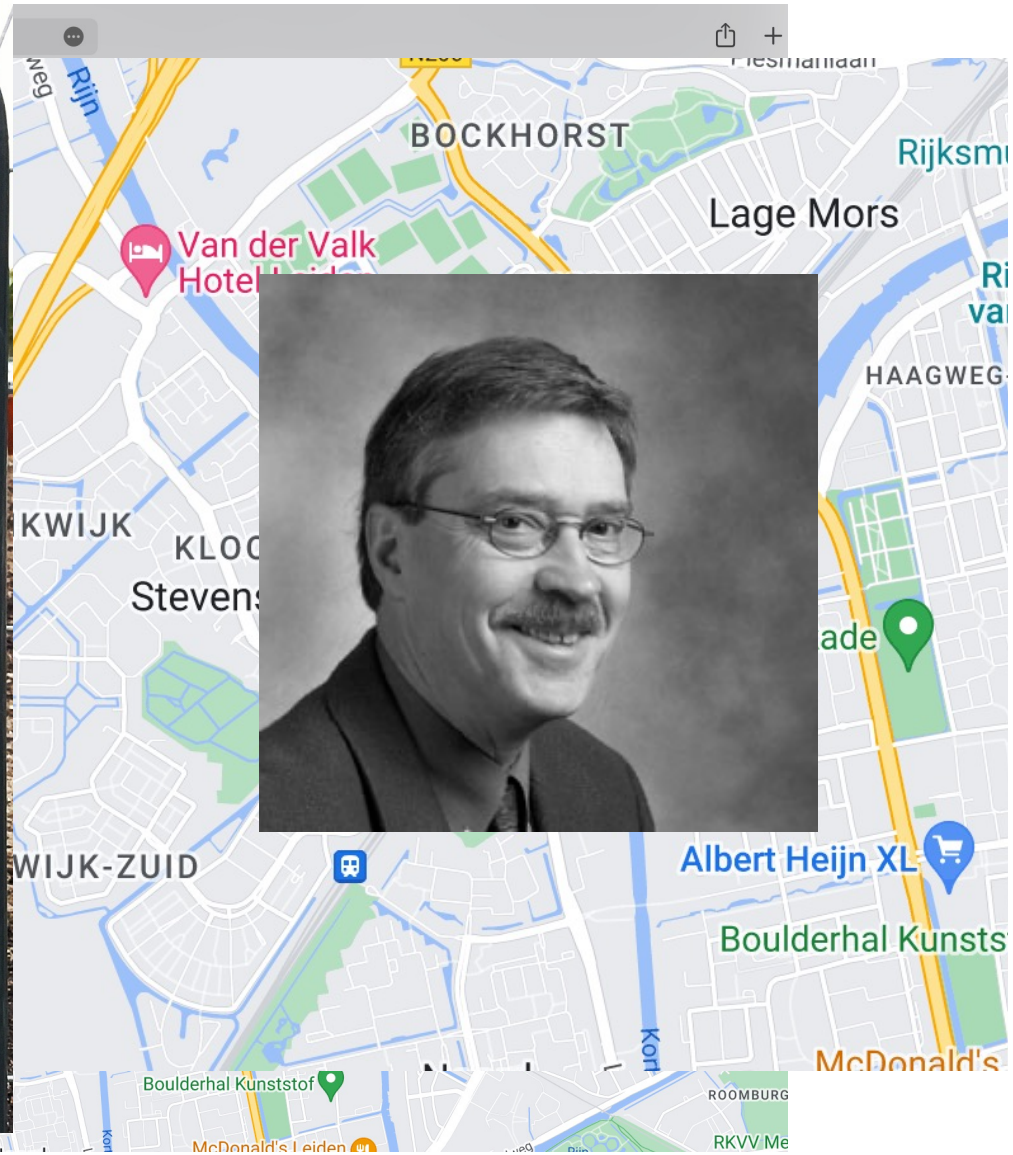
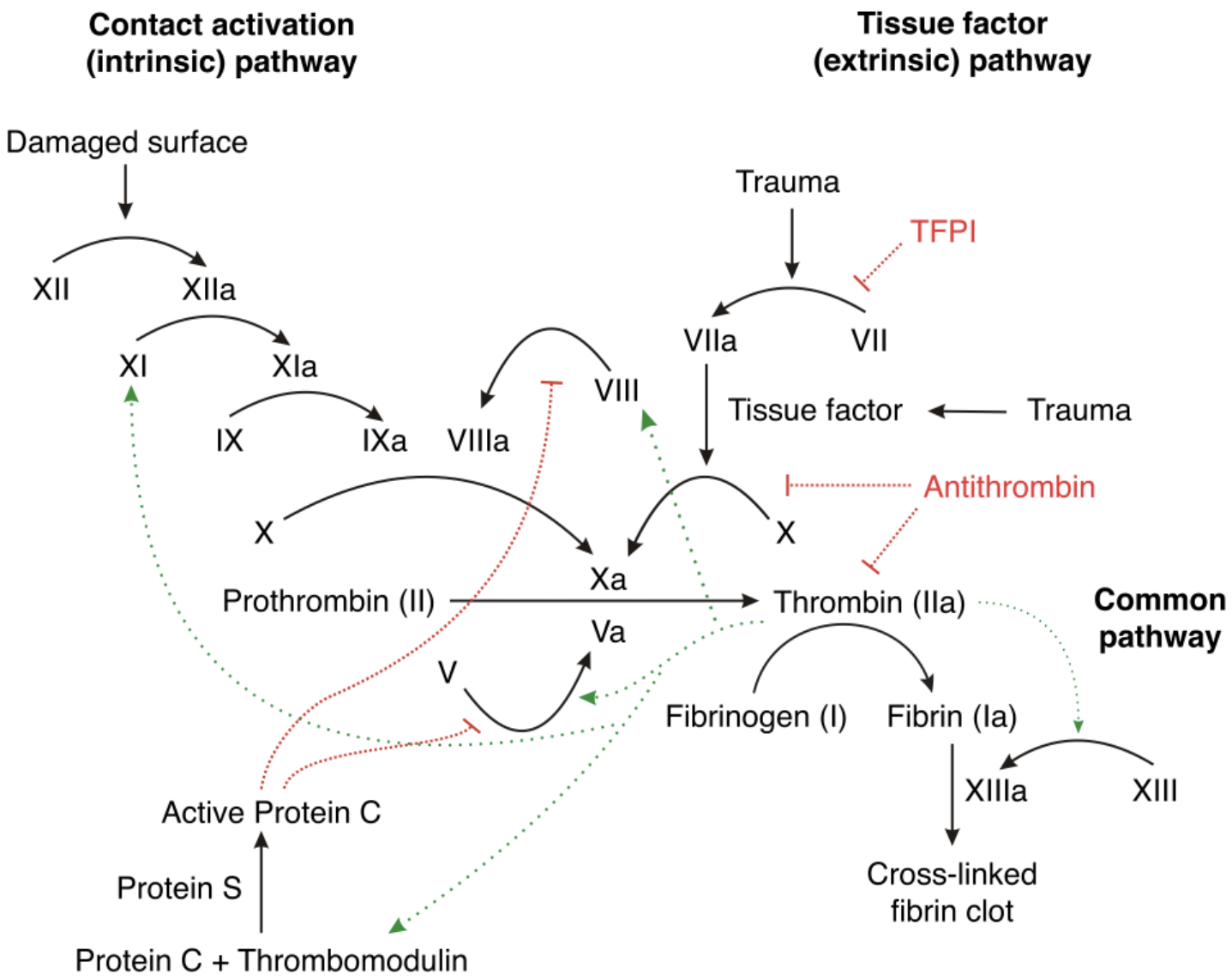


Pro- en anticoagulante factoren in de bloedstolling (Wikipedia)



Erfelijke factoren bij trombose in 1992

	Prevalentie	Risico
Antitrombine deficiëntie	0.02%	?
Proteïne C deficiëntie	0.2-0.4%	7-10x
Proteïne S deficiëntie	?	?

Erfelijke factoren bij trombose in 1992

RAPID COMMUNICATION

The Spectrum of Genetic Defects in a Panel of 40 Dutch Families With Symptomatic Protein C Deficiency Type I: Heterogeneity and Founder Effects

By P.H. Reitsma, S.R. Poort, C.F. Allaart, E. Briët, and R.M. Bertina

Heterozygosity for protein C deficiency is associated with thromboembolic episodes, but clinical symptoms are nonrandomly distributed among protein C deficient families. This finding has led to the provisional definition of clinically dominant and clinically recessive protein C deficiency. We report here the molecular basis of hereditary, clinically dominant protein C deficiency in a panel of 40 Dutch probands from apparently independent families. All but one subject was a heterozygote for a point mutation in the protein C gene. These 39 subjects shared 15 mutations, six of which occurred in more than one proband (between two and nine). The diversity in the 15 mutations, together with the observation that the most frequent Dutch mutation was also found in a Swedish family with clinically recessive protein C deficiency, makes it unlikely that the molecular basis of protein C deficiency will be different between the clinically dominant and recessive forms. The recurrence of one of the mutations is most likely due to a founder effect, which suggests that when an additional hereditary factor is involved in the clinical severity of protein C deficiency this factor may remain linked to the protein C gene over many generations.

THE HUMAN BLOOD coagulation cascade is downregulated by a variety of natural anticoagulant mechanisms. Among these mechanisms is the so-called "protein C anticoagulant pathway."[1] This pathway is initiated when thrombin (generated in the coagulation cascade) binds to the endothelial membrane receptor thrombomodulin. The resulting complex activates the zymogen protein C. Activated protein C in turn inactivates the procoagulant cofac-

These findings contrast sharply with two sets of data that do not support a strong association between heterozygosity for protein C deficiency and thrombotic disease. First, there is the observation that in many instances severely affected homozygous infants were born from heterozygous parents who have neither a personal predisposition to thrombosis nor a family history of thrombosis.[2-4] Second, the measurement of protein C levels in a large panel of 4,723 healthy

‘Activated protein C resistance’ (APC resistentie)

Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 1004–1008, February 1993
Medical Sciences

Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: Prediction of a cofactor to activated protein C

(protein S/thrombosis/blood coagulation/anticoagulation)

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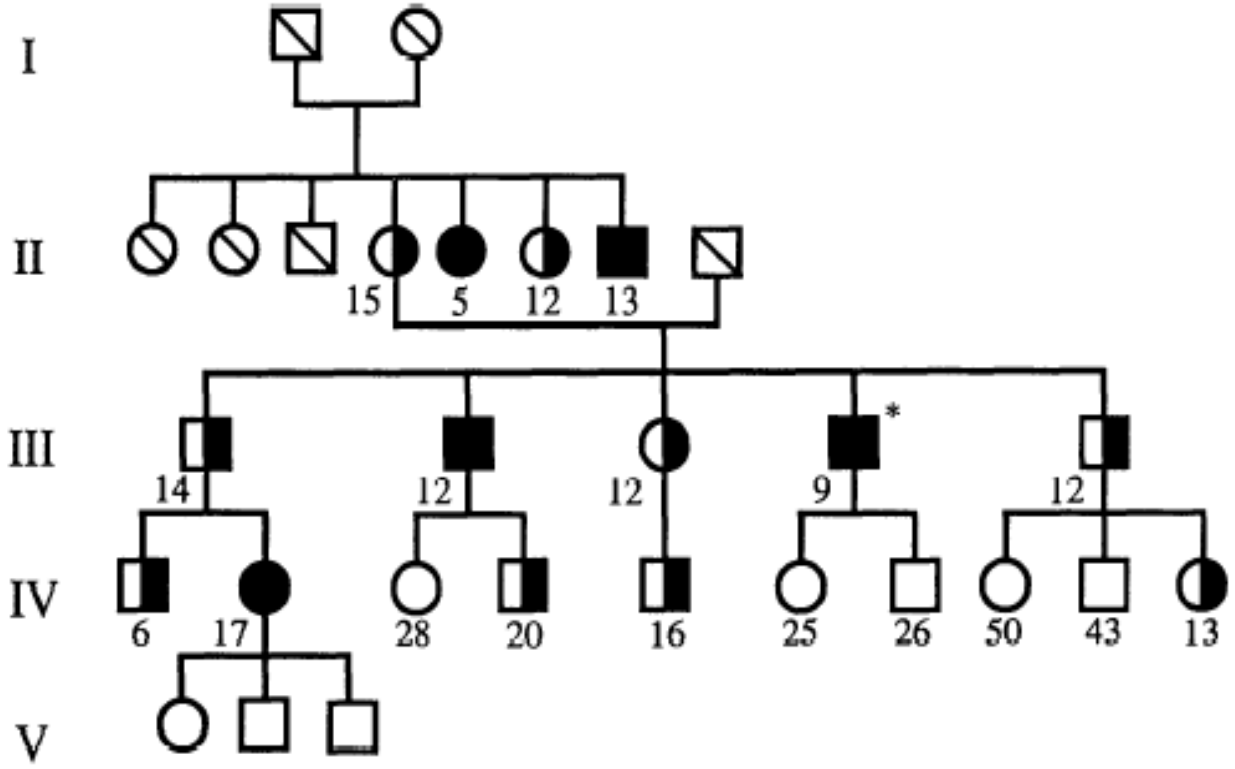
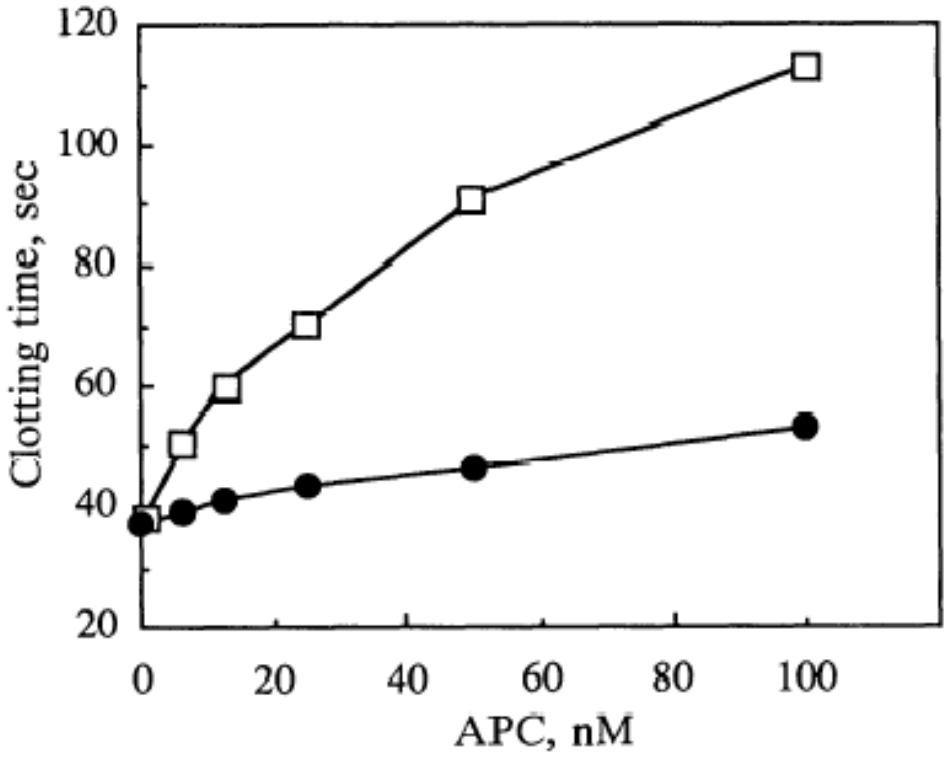
*Department of Clinical Chemistry and †Department for Coagulation Disorders, University of Lund, Malmö General Hospital, S-21401 Malmö, Sweden; and §Department of Medicine, Ryhov Hospital, S-55185 Jönköping, Sweden

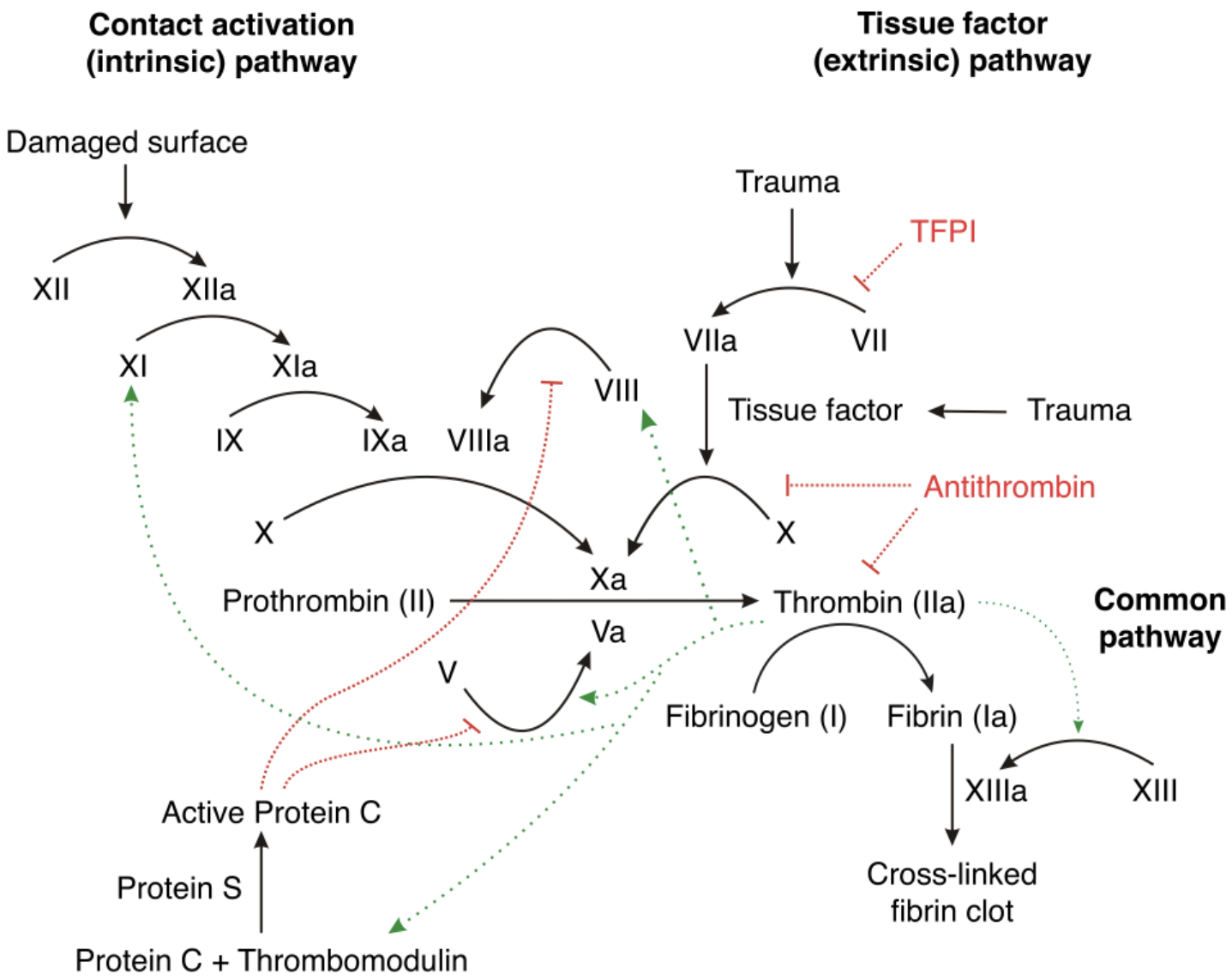
Communicated by Jan G. Waldenström, October 15, 1992

De resultaten



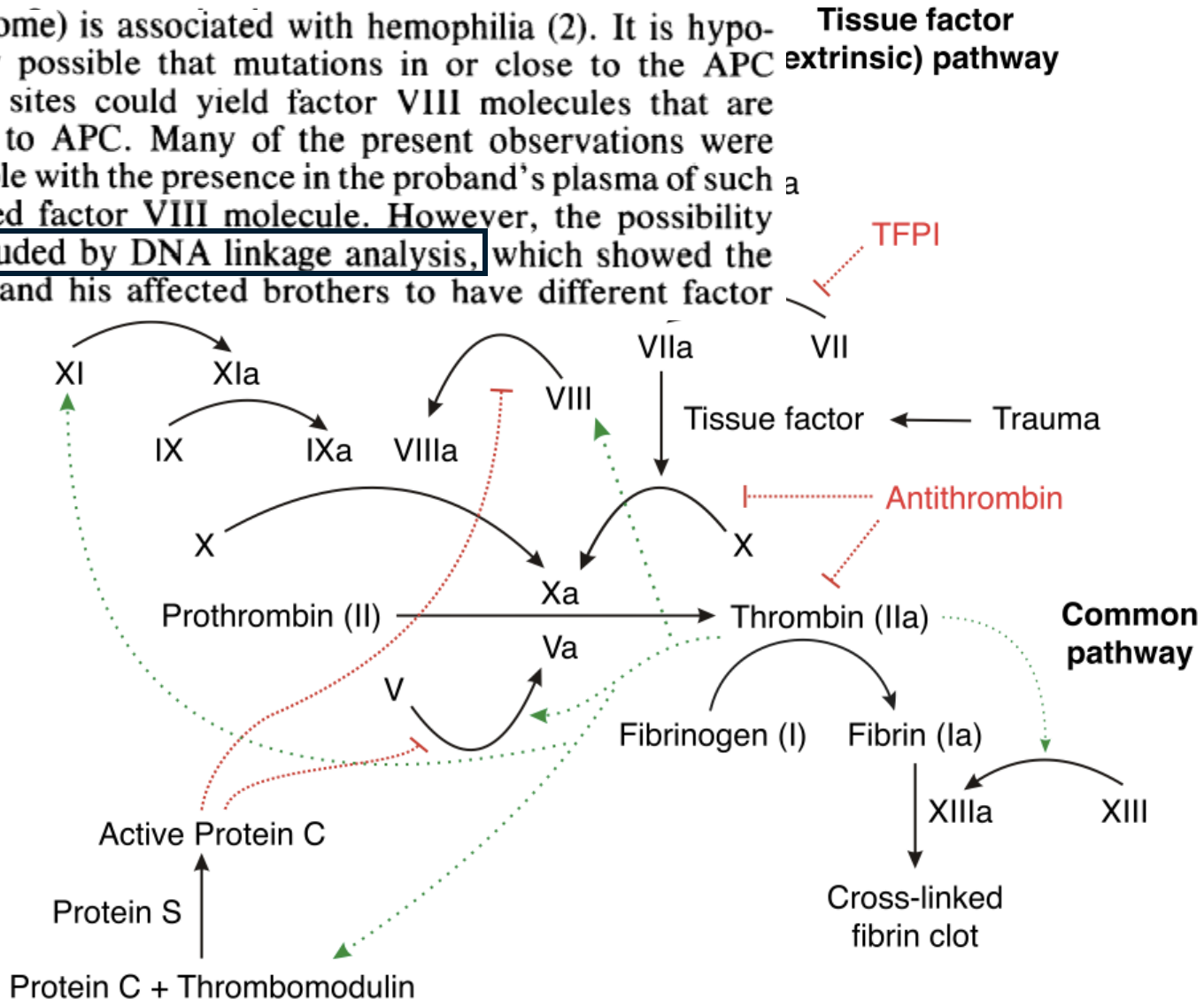


Is stollingsfactor factor VIII of V betrokken?



Is stollingsfactor factor VIII of V betrokken?

chromosome) is associated with hemophilia (2). It is hypothetically possible that mutations in or close to the APC cleavage sites could yield factor VIII molecules that are resistant to APC. Many of the present observations were compatible with the presence in the proband's plasma of such a modified factor VIII molecule. However, the possibility was excluded by DNA linkage analysis, which showed the proband and his affected brothers to have different factor



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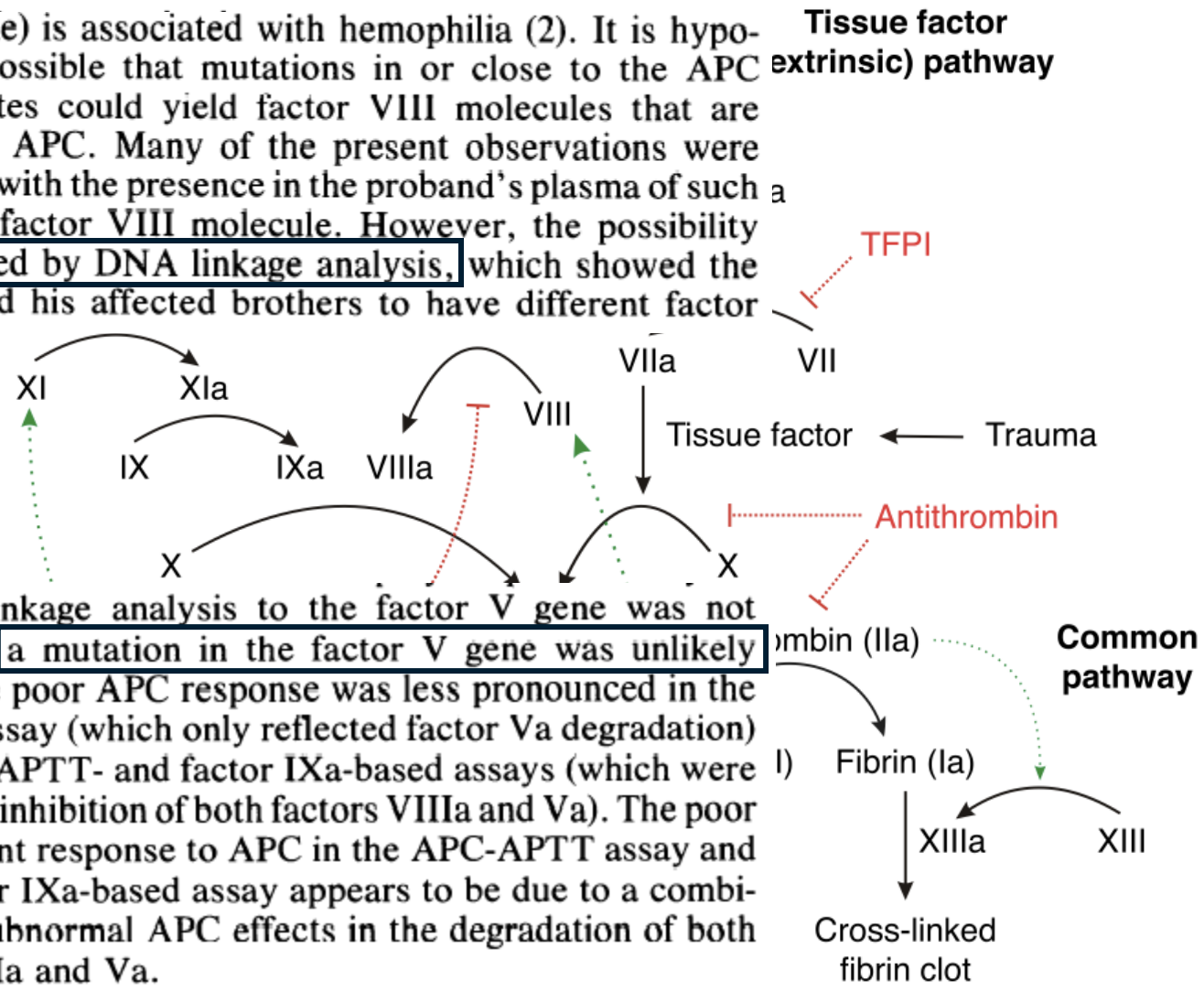
Although linkage analysis to the factor V gene was not performed, a mutation in the factor V gene was unlikely because the poor APC response was less pronounced in the factor Xa assay (which only reflected factor Va degradation) than in the APTT- and factor IXa-based assays (which were sensitive to inhibition of both factors VIIIa and Va). The poor anticoagulant response to APC in the APC-APTT assay and in the factor IXa-based assay appears to be due to a combination of subnormal APC effects in the degradation of both factors VIIIa and Va.



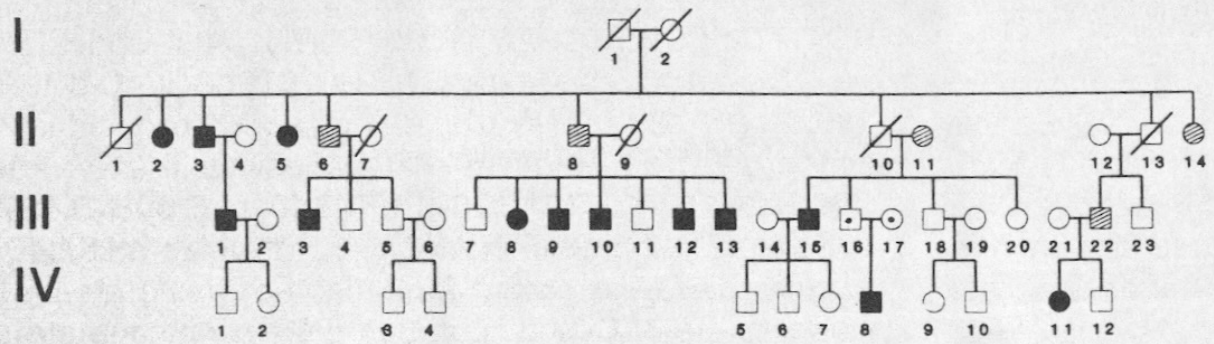
Protein C + Thrombomodulin

Het antwoord is:

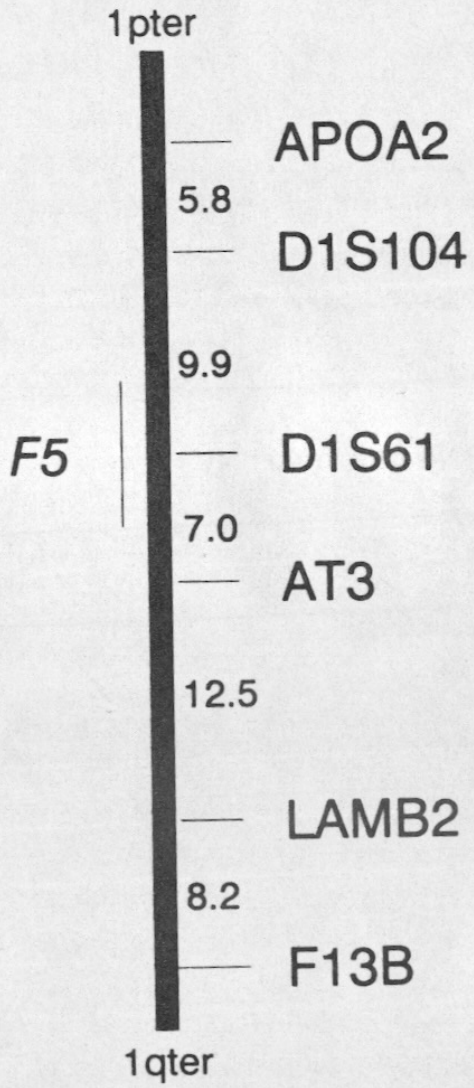
The inherited poor anticoagulant response to APC described here cannot be explained by the currently accepted scheme of the protein C anticoagulant system. On the basis of results presented in this paper, it would appear to be reasonable to hypothesize the presence in normal plasma of a previously unrecognized cofactor to APC. The poor anticoagulant response to APC found in the proband and many of his relatives appears to be best explained by an inherited deficiency of such a cofactor. Although elucidation of the

Analyse van een familie met APC-resistentie, oktober 1993

a



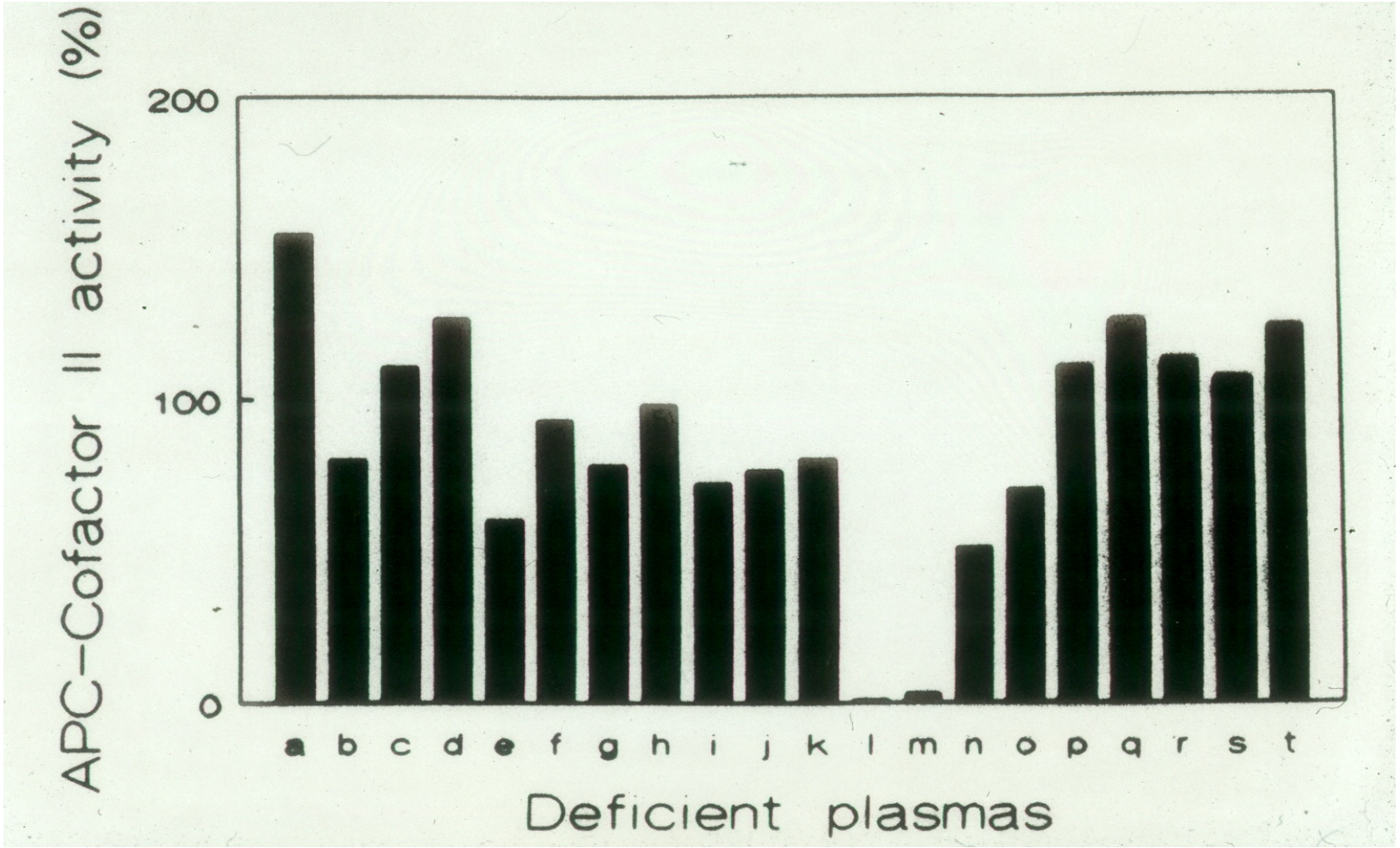
b



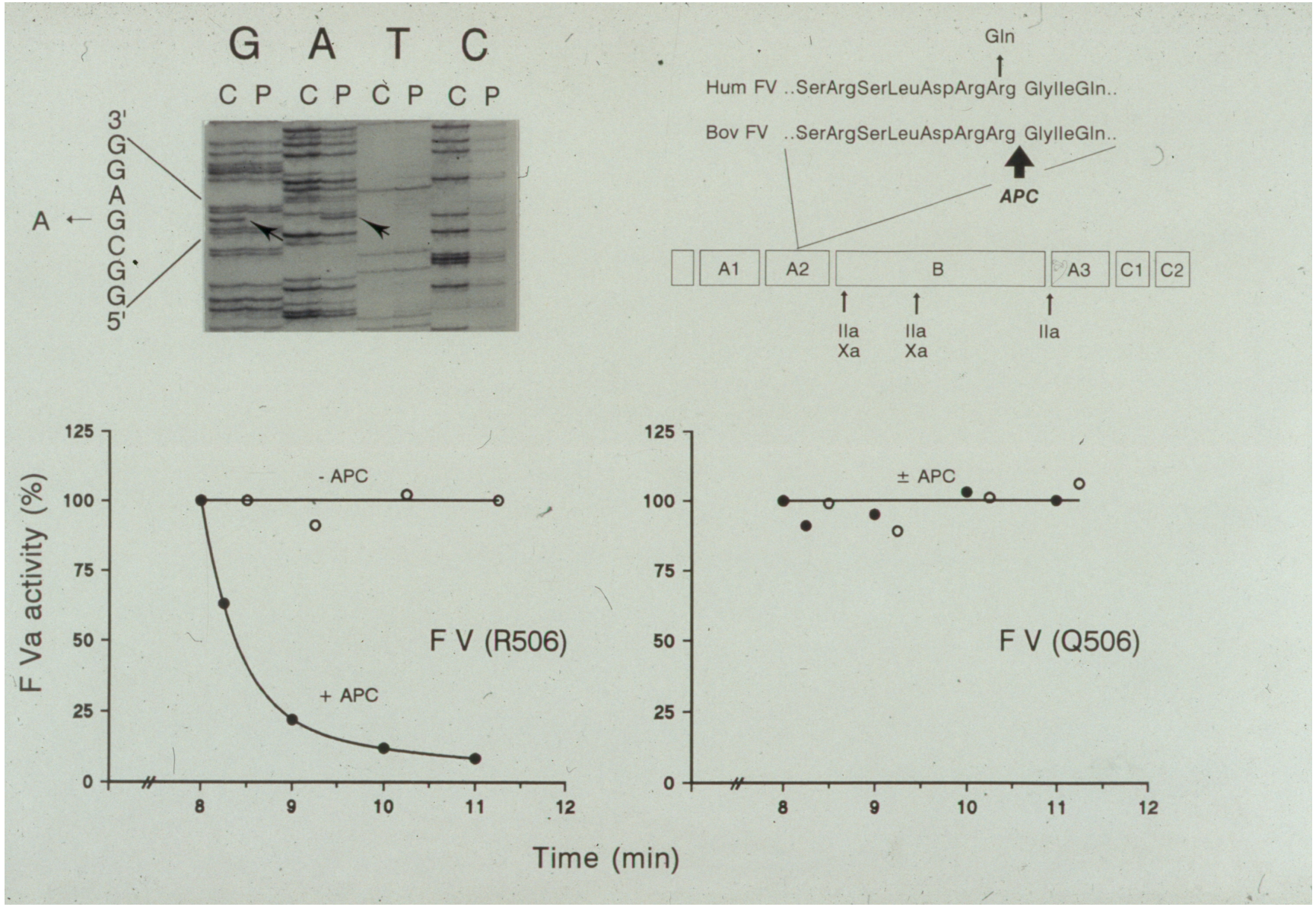
c

	Two-point lod score at different θ values									
Locus/marker	0.0	0.001	0.01	0.05	0.10	0.20	0.30	0.40	Z max	θ
APOA2	-∞	-3.162	-1.181	0.119	0.617	0.965	0.833	0.432	0.974	0.22
D1S104	0.952	0.953	0.972	1.160	1.272	1.137	0.762	0.304	1.276	0.11
D1S61	7.270	7.258	7.152	6.668	6.034	4.659	3.114	1.393	7.270	0.00
LAMB2	-∞	0.006	0.963	1.463	1.503	1.246	0.827	0.356	1.513	0.08
F13B	-∞	-0.812	1.350	2.862	3.152	2.776	1.919	0.829	3.152	0.11

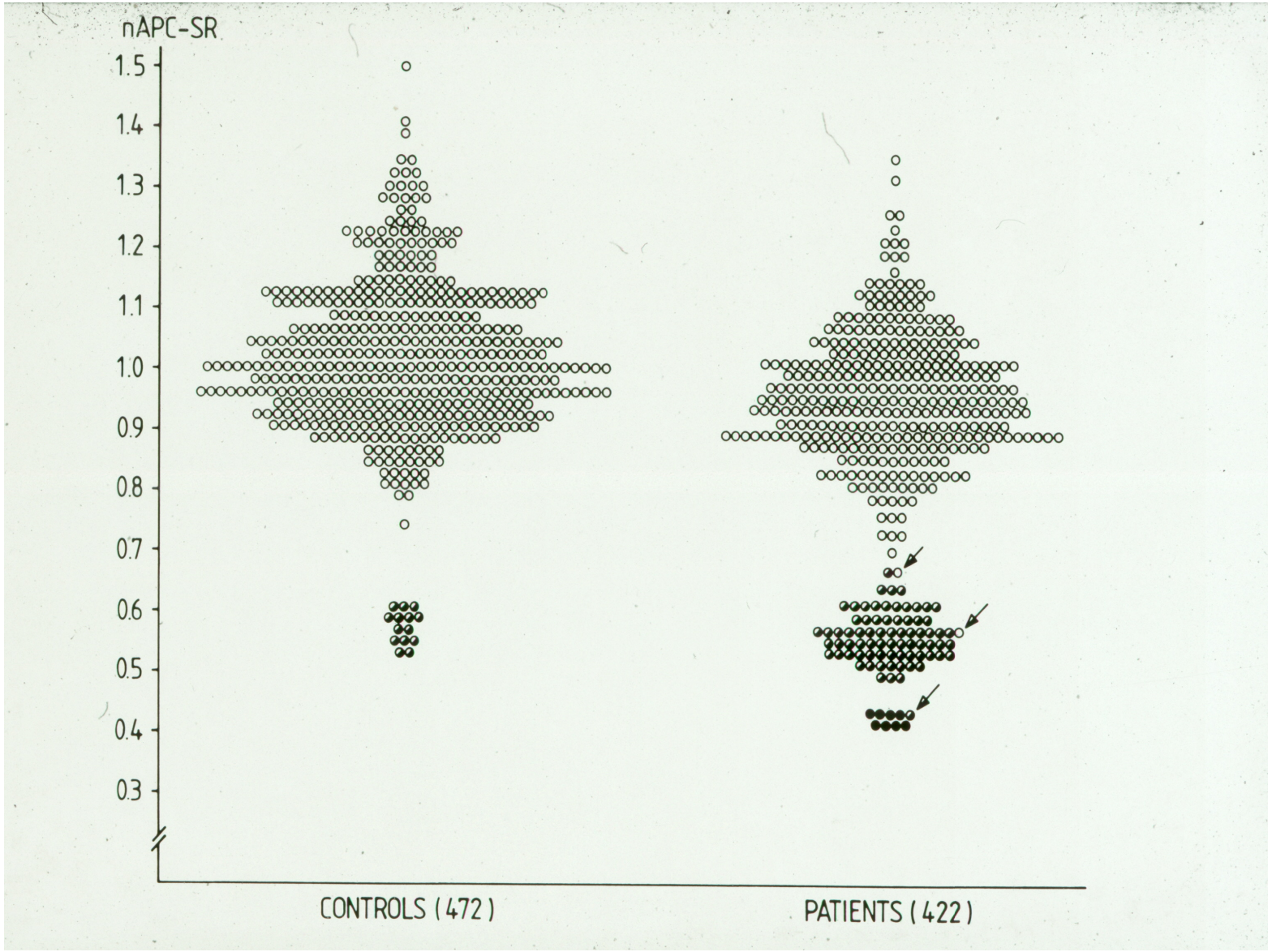
Mengproeven, oktober 1993



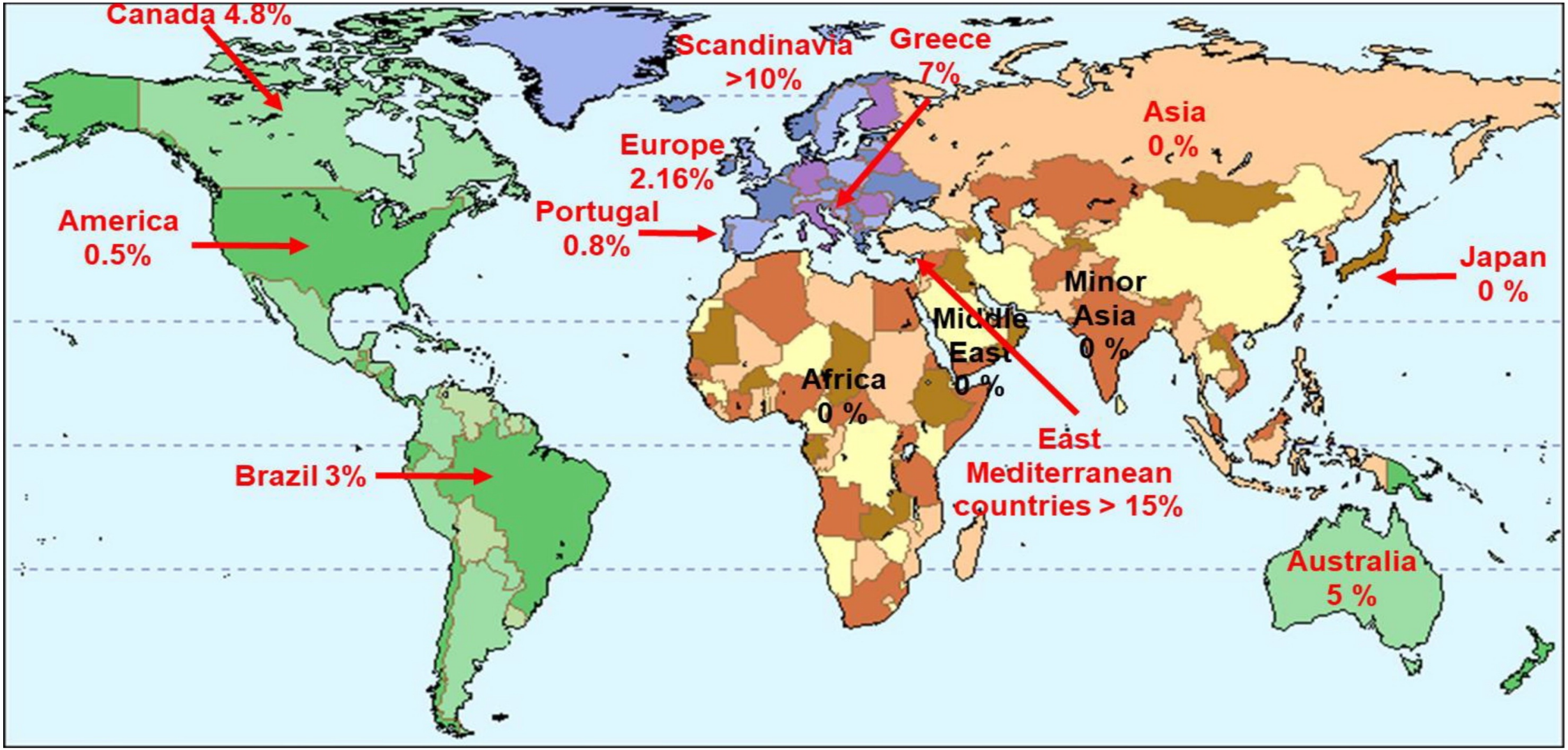
Factor V Leiden mutatie gevonden, oktober 1993



Prevalentie factor V Leiden mutatie in patiënten en controles (LETS)



Verdeling van factor V Leiden over de wereld



Wedstrijd

Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994 May 5; 369(6475):64-7.

Greengard JS, Sun X, Xu X, Fernandez JA, Griffin JH, Evatt B. Activated protein C resistance caused by Arg506Gln mutation in factor Va. Lancet. 1994 May 28; 343(8909):1361-2.

Voorberg J, Roelse J, Koopman R, Büller H, Berends F, ten Cate JW, Mertens K, van Mourik JA. Association of idiopathic venous thromboembolism with singlepoint-mutation at Arg506 of factor V. Lancet. 1994 Jun 8; 343(8912):1535-6.

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Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994 May 5; 369(6475):64-7. **3558 CITATIES**

Greengard JS, Sun X, Xu X, Fernandez JA, Griffin JH, Evatt B. Activated protein C resistance caused by Arg506Gln mutation in factor Va. Lancet. 1994 May 28; 343(8909):1361-2. **254 CITATIES**

Voorberg J, Roelse J, Koopman R, Büller H, Berends F, ten Cate JW, Mertens K, van Mourik JA. Association of idiopathic venous thromboembolism with single point-mutation at Arg506 of factor V. Lancet. 1994 Jun 8; 343(8912):1535-6. **437 CITATIES**

Factor V Leiden patent

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 696 325 B1

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13.05.1998 Bulletin 1998/20

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(22) Date of filing: **14.02.1995**

(51) Int Cl.[6]: **C12Q 1/68**, C07K 14/745, G01N 33/86

(86) International application number:
PCT/EP95/00553

(87) International publication number:
WO 95/21938 (17.08.1995 Gazette 1995/35)

(54) **A METHOD FOR SCREENING FOR THE PRESENCE OF A GENETIC DEFECT ASSOCIATED WITH THROMBOSIS AND/OR POOR ANTICOAGULANT RESPONSE TO ACTIVATED PROTEIN C**

VERFAHREN ZUM NACHWEIS EINES GENETISCHEN DEFEKTES, ASSOZIERT MIT THROMBOSE UND/ODER MANGELHAFTER ANTICOAGULANZ-REAKTION AUF AKTIVIERTEM PROTEIN C

PROCEDE DE DEPISTAGE D'UNE ANOMALIE GENETIQUE ASSSOCIE A LA TROMBOSE ET/OU A UNE MAUVAISE REPONSE ANTICOAGULANTE A LA PROTEINE C ACTIVEE

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **14.02.1994 EP 94200377**

(43) Date of publication of application:
14.02.1996 Bulletin 1996/07

(60) Divisional application: **97201766.9 / 0 807 691**

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  NL-2333 XJ Leiden (NL)

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- **THE LANCET, vol. 342,no. 8886, 1993 LONDON GB, pages 1503-1506, T.KOSTER ET AL. 'Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden thrombophilia study' cited in the application**
- **THE JOURNAL OF IMMUNOLOGY, vol. 150,no. 7, 1993 BALTIMORE US, pages 2992-3001, N.L.L.SHEN ET AL. 'The serine protease cofactor factor V is synthesized by lymphocytes' cited in the application**
- **BLOOD, vol. 82,no. 10, suppl.1, November 1993 NEW YORK US, page 58A M.KALAFATIS ET AL. 'Membrane-bound human factor Va is inactivated by activated protein C after cleavage of the heavy chain at Arg506 and Arg306' cited in the application**
- **PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 84, 1987 WASHINGTON US, pages 4846-4850, R.J.JENNY ET AL. 'Complete cDNA and derived amino acid sequence of human factor V' cited in the application**
- **BIOTECHNOLOGY, vol. 8, April 1990 NEW YORK US, pages 291-294, L.VAN BRUNT 'Amplifying**

Implicaties

- Grote invloed op het denken over erfelijke risicofactoren voor trombose
- Veel aandacht gegenereerd voor interacties tussen erfelijke en niet-erfelijke risicofactoren
- Nut voor primaire preventie van trombose beperkt?