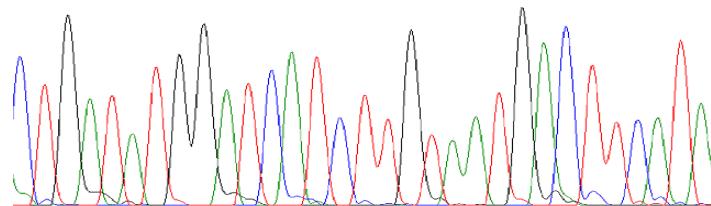


**IDENTIFICACIÓ DELS FACTORS GENÈTICS QUE
DETERMINEN LA VARIABILITAT DELS NIVELLS
DE FVII A LA POBLACIÓ ESPANYOLA**

Resultats del Projecte GAIT



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BIBLIOGRAFIA

- Alexander B, Goldstein R, Landwehr G, Cook CD. 1951. Congenital SPCA deficiency: a hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions. *J Clin Invest* 30(6):596-608.
- Almasy L, Blangero J. 1998. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet* 62(5):1198-211.
- Almasy L, MacCluer JW. 2002. Association studies of vascular phenotypes: how and why? *Arterioscler Thromb Vasc Biol* 22(7):1055-7.
- Almasy L, Terwilliger JD, Nielsen D, Dyer TD, Zaykin D, Blangero J. 2001. GAW12: simulated genome scan, sequence, and family data for a common disease. *Genet Epidemiol* 21 Suppl 1:S332-8.
- Almasy L, Williams JT, Dyer TD, Blangero J. 1999. Quantitative trait locus detection using combined linkage/disequilibrium analysis. *Genet Epidemiol* 17 Suppl 1:S31-6.
- Amos CI. 1994. Robust variance-components approach for assessing genetic linkage in pedigrees. *Am J Hum Genet* 54(3):535-43.
- Arbini AA, Bodkin D, Lopaciuk S, Bauer KA. 1994. Molecular analysis of Polish patients with factor VII deficiency. *Blood* 84(7):2214-20.
- Bajaj SP, Rapaport SI, Brown SF. 1981. Isolation and characterization of human factor VII. Activation of factor VII by factor Xa. *J Biol Chem* 256(1):253-9.
- Bajzar L. 2000. Thrombin activatable fibrinolysis inhibitor and an antifibrinolytic pathway. *Arterioscler Thromb Vasc Biol* 20(12):2511-8.
- Bajzar L, Manuel R, Nesheim ME. 1995. Purification and characterization of TAFI, a thrombin-activable fibrinolysis inhibitor. *J Biol Chem* 270(24):14477-84.
- Balleisen L, Assmann G, Bailey J, Epping PH, Schulte H, van de Loo J. 1985. Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population--II. Baseline data on the

- relation to blood pressure, blood glucose, uric acid, and lipid fractions. *Thromb Haemost* 54(3):721-3.
- Banner DW, D'Arcy A, Chene C, Winkler FK, Guha A, Konigsberg WH, Nemerson Y, Kirchhofer D. 1996. The crystal structure of the complex of blood coagulation factor VIIa with soluble tissue factor. *Nature* 380(6569):41-6.
- Bates SM, Ginsberg JS. 2004. Clinical practice. Treatment of deep-vein thrombosis. *N Engl J Med* 351(3):268-77.
- Bauer KA, Kass BL, ten Cate H, Hawiger JJ, Rosenberg RD. 1990. Factor IX is activated in vivo by the tissue factor mechanism. *Blood* 76(4):731-6.
- Baumgartner HR. 1973. The role of blood flow in platelet adhesion, fibrin deposition, and formation of mural thrombi. *Microvasc Res* 5(2):167-79.
- Beato M. 1989. Gene regulation by steroid hormones. *Cell* 56(3):335-44.
- Beavers WR, Voeller MN. 1983. Family models: comparing and contrasting the Olson Circumplex Model with the Beavers Systems Model. *Fam Process* 22(1):85-98.
- Berkner K, Busby S, Davie E, Hart C, Insley M, Kisiel W, Kumar A, Murray M, O'Hara P, Woodbury R and others. 1986. Isolation and expression of cDNAs encoding human factor VII. *Cold Spring Harb Symp Quant Biol* 51 Pt 1:531-41.
- Bernardi F, Castaman G, Redaelli R, Pinotti M, Lunghi B, Rodeghiero F, Marchetti G. 1994. Topologically equivalent mutations causing dysfunctional coagulation factors VII (294Ala-->Val) and X (334Ser-->Pro). *Hum Mol Genet* 3(7):1175-7.
- Bernardi F, Marchetti G, Pinotti M, Arcieri P, Baroncini C, Papacchini M, Zepponi E, Ursicino N, Chiarotti F, Mariani G. 1996. Factor VII gene polymorphisms contribute about one third of the factor VII level variation in plasma. *Arterioscler Thromb Vasc Biol* 16(1):72-6.
- Bernardi F, Patracchini P, Gemmati D, Ferrati M, Arcieri P, Papacchini M, Redaelli R, Baudo F, Mariani G, Marchetti G. 1993. Molecular analysis of factor VII deficiency in Italy: a frequent mutation (FVII Lazio) in a repeated intronic region. *Hum Genet* 92(5):446-50.

- Bertina RM. 2001. Genetic approach to thrombophilia. *Thromb Haemost* 86(1):92-103.
- Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. 1994. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 369(6475):64-7.
- Blangero J, Williams JT, Almasy L. 2003. Novel family-based approaches to genetic risk in thrombosis. *J Thromb Haemost* 1(7):1391-7.
- Blann AD, Lip GY. 2001. Virchow's triad revisited: the importance of soluble coagulation factors, the endothelium, and platelets. *Thromb Res* 101(4):321-7.
- Boerwinkle E, Ellsworth DL, Hallman DM, Biddinger A. 1996. Genetic analysis of atherosclerosis: a research paradigm for the common chronic diseases. *Hum Mol Genet* 5 Spec No:1405-10.
- Bolivar F, Rodriguez RL, Betlach MC, Boyer HW. 1977a. Construction and characterization of new cloning vehicles. I. Ampicillin-resistant derivatives of the plasmid pMB9. *Gene* 2(2):75-93.
- Bolivar F, Rodriguez RL, Greene PJ, Betlach MC, Heyneker HL, Boyer HW. 1977b. Construction and characterization of new cloning vehicles. II. A multipurpose cloning system. *Gene* 2(2):95-113.
- Borensztajn K, Sobrier ML, Fischer AM, Chafa O, Amselem S, Tapon-Bretaudiere J. 2003. Factor VII gene intronic mutation in a lethal factor VII deficiency: effects on splice-site selection. *Blood* 102(2):561-3.
- Bovill EG, Hassstedt SJ, Leppert MF, Long GL. 1999. Hereditary thrombophilia as a model for multigenic disease. *Thromb Haemost* 82(2):662-6.
- Bozzini C, Girelli D, Bernardi F, Ferraresi P, Olivieri O, Pinotti M, Martinelli N, Manzato F, Friso S, Villa G and others. 2004. Influence of polymorphisms in the factor VII gene promoter on activated factor VII levels and on the risk of myocardial infarction in advanced coronary atherosclerosis. *Thromb Haemost* 92(3):541-9.

- Broze G. 1994. The tissue factor pathway of coagulation: factor VII, tissue factor, and tissue factor pathway inhibitor. In: Bloom AL FC, Thomas DP, Tuddenham EGD, editor. *Haemostasis and Thrombosis*. Edinburgh: Churchill Livingstone. p 349-377.
- Broze GJ, Jr., Majerus PW. 1980. Purification and properties of human coagulation factor VII. *J Biol Chem* 255(4):1242-7.
- Bucher P. 1990. Weight matrix descriptions of four eukaryotic RNA polymerase II promoter elements derived from 502 unrelated promoter sequences. *J Mol Biol* 212(4):563-78.
- Camerer E, Rottingen JA, Gjernes E, Larsen K, Skartlien AH, Iversen JG, Prydz H. 1999. Coagulation factors VIIa and Xa induce cell signaling leading to up-regulation of the egr-1 gene. *J Biol Chem* 274(45):32225-33.
- Cardon LR, Abecasis GR. 2003. Using haplotype blocks to map human complex trait loci. *Trends Genet* 19(3):135-40.
- Carew JA, Basso F, Miller GJ, Hawe E, Jackson AA, Humphries SE, Bauer KA. 2003a. A functional haplotype in the 5' flanking region of the factor VII gene is associated with an increased risk of coronary heart disease. *J Thromb Haemost* 1(10):2179-85.
- Carew JA, Jackson AA, Bauer KA. 2003b. ARP1 interacts with the 5' flanking region of the coagulation factor VII gene. *J Thromb Haemost* 1(6):1220-7.
- Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, Pober JS, Wick TM, Konkle BA, Schwartz BS and others. 1998. Endothelial cells in physiology and in the pathophysiology of vascular disorders. *Blood* 91(10):3527-61.
- Comuzzie AG, Hixson JE, Almasy L, Mitchell BD, Mahaney MC, Dyer TD, Stern MP, MacCluer JW, Blangero J. 1997. A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2. *Nat Genet* 15(3):273-6.
- Corral J, Gonzalez-Conejero R, Lozano ML, Rivera J, Vicente V. 1998. Genetic polymorphisms of factor VII are not associated with arterial thrombosis. *Blood Coagul Fibrinolysis* 9(3):267-72.

- Corral J, Iniesta JA, Gonzalez-Conejero R, Villalon M, Vicente V. 2001. Polymorphisms of clotting factors modify the risk for primary intracranial hemorrhage. *Blood* 97(10):2979-82.
- Curran JE, Jowett JB, Elliott KS, Gao Y, Gluschenko K, Wang J, Abel Azim DM, Cai G, Mahaney MC, Comuzzie AG and others. 2005. Genetic variation in selenoprotein S influences inflammatory response. *Nat Genet* 37(11):1234-41.
- Dahlback B. 1995. The protein C anticoagulant system: inherited defects as basis for venous thrombosis. *Thromb Res* 77(1):1-43.
- Dahlback B. 2000. Blood coagulation. *Lancet* 355(9215):1627-32.
- Dahlback B, Villoutreix BO. 2005. The anticoagulant protein C pathway. *FEBS Lett* 579(15):3310-6.
- Davie EW, Fujikawa K, Kurachi K, Kisiel W. 1979. The role of serine proteases in the blood coagulation cascade. *Adv Enzymol Relat Areas Mol Biol* 48:277-318.
- Davie EW, Ichinose A, Leytus SP. 1986. Structural features of the proteins participating in blood coagulation and fibrinolysis. *Cold Spring Harb Symp Quant Biol* 51 Pt 1:509-14.
- Davie EW, Ratnoff OD. 1964. Waterfall Sequence for Intrinsic Blood Clotting. *Science* 145:1310-2.
- Dell'Acqua G, Iacoviello L, D'Orazio A, Di Bitondo R, Di Castelnuovo A, Donati MB. 1997. A polymorphic cluster in the 5' region of the human coagulation factor VII gene: detection, frequency, and linkage disequilibrium. *Thromb Res* 88(5):445-8.
- Di Bitondo R, Hall AJ, Peake IR, Iacoviello L, Winship PR. 2002. Oestrogenic repression of human coagulation factor VII expression mediated through an oestrogen response element sequence motif in the promoter region. *Hum Mol Genet* 11(7):723-31.
- Di Castelnuovo A, D'Orazio A, Amore C, Falanga A, Donati MB, Iacoviello L. 2000. The decanucleotide insertion/deletion polymorphism in the promoter region of the coagulation factor VII gene and the risk of familial myocardial infarction. *Thromb Res* 98(1):9-17.

- Di Castelnuovo A, D'Orazio A, Amore C, Falanga A, Kluft C, Donati MB, Iacoviello L. 1998. Genetic modulation of coagulation factor VII plasma levels: contribution of different polymorphisms and gender-related effects. *Thromb Haemost* 80(4):592-7.
- Di Scipio RG, Hermodson MA, Yates SG, Davie EW. 1977. A comparison of human prothrombin, factor IX (Christmas factor), factor X (Stuart factor), and protein S. *Biochemistry* 16(4):698-706.
- Duggirala R, Blangero J, Almasy L, Dyer TD, Williams KL, Leach RJ, O'Connell P, Stern MP. 1999. Linkage of type 2 diabetes mellitus and of age at onset to a genetic location on chromosome 10q in Mexican Americans. *Am J Hum Genet* 64(4):1127-40.
- Egeberg O. 1965. Inherited Antithrombin Deficiency Causing Thrombophilia. *Thromb Diath Haemorrh* 13:516-30.
- Endler G, Mannhalter C. 2003. Polymorphisms in coagulation factor genes and their impact on arterial and venous thrombosis. *Clin Chim Acta* 330(1-2):31-55.
- Erdmann D, Heim J. 1995. Orphan nuclear receptor HNF-4 binds to the human coagulation factor VII promoter. *J Biol Chem* 270(39):22988-96.
- Eriksson-Berg M, Deguchi H, Hawe E, Scanavini D, Orth-Gomer K, Schenck-Gustafsson K, Humphries SE, Silveira A, Hamsten A. 2005. Influence of factor VII gene polymorphisms and environmental factors on plasma coagulation factor VII concentrations in middle-aged women with and without manifest coronary heart disease. *Thromb Haemost* 93(2):351-8.
- Esmon CT. 1992. The protein C anticoagulant pathway. *Arterioscler Thromb* 12(2):135-45.
- Esmon CT, Owen WG. 1981. Identification of an endothelial cell cofactor for thrombin-catalyzed activation of protein C. *Proc Natl Acad Sci U S A* 78(4):2249-52.
- Fair DS. 1983. Quantitation of factor VII in the plasma of normal and warfarin-treated individuals by radioimmunoassay. *Blood* 62(4):784-91.
- Falconer M. 1996. Introduction to quantitative genetics. Essex: Longman Group Ltd.

- Fejerman L, Bouzekri N, Wu X, Adeyemo A, Luke A, Zhu X, Ward R, Cooper RS. 2004. Association between evolutionary history of angiotensinogen haplotypes and plasma levels. *Hum Genet* 115(4):310-8.
- Feng D, Tofler GH, Larson MG, O'Donnell CJ, Lipinska I, Schmitz C, Sutherland PA, Johnstone MT, Muller JE, D'Agostino RB and others. 2000. Factor VII gene polymorphism, factor VII levels, and prevalent cardiovascular disease: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 20(2):593-600.
- Fisher CL, Pei GK. 1997. Modification of a PCR-based site-directed mutagenesis method. *Biotechniques* 23(4):570-1, 574.
- Franco RF, Reitsma PH. 2001. Genetic risk factors of venous thrombosis. *Hum Genet* 109(4):369-84.
- Fukudome K, Esmon CT. 1994. Identification, cloning, and regulation of a novel endothelial cell protein C/activated protein C receptor. *J Biol Chem* 269(42):26486-91.
- Furie B, Furie BC. 1988. The molecular basis of blood coagulation. *Cell* 53(4):505-18.
- Furie B, Furie BC. 1992. Molecular and cellular biology of blood coagulation. *N Engl J Med* 326(12):800-6.
- Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M and others. 2002. The structure of haplotype blocks in the human genome. *Science* 296(5576):2225-9.
- Gailani D, Broze GJ, Jr. 1991. Factor XI activation in a revised model of blood coagulation. *Science* 253(5022):909-12.
- Gambaro G, Anglani F, D'Angelo A. 2000. Association studies of genetic polymorphisms and complex disease. *Lancet* 355(9200):308-11.
- Gilgenkrantz S, Briquel ME, Andre E, Alexandre P, Jalbert P, Le Marec B, Pouzol P, Pommereuil M. 1986. Structural genes of coagulation factors VII and X located on 13q34. *Ann Genet* 29(1):32-5.

- Girelli D, Russo C, Ferraresi P, Olivieri O, Pinotti M, Friso S, Manzato F, Mazzucco A, Bernardi F, Corrocher R. 2000. Polymorphisms in the factor VII gene and the risk of myocardial infarction in patients with coronary artery disease. *N Engl J Med* 343(11):774-80.
- Goldstein DB, Weale ME. 2001. Population genomics: linkage disequilibrium holds the key. *Curr Biol* 11(14):R576-9.
- Gonzalez-Neira XK, Oscar Lao, Francesc Calafell, Arcadi Navarro,, David Comas HC, Suzannah Bumpstead, Jilur Ghori, Sarah Hunt, Panos, Deloukas ID, Lon R. Cardon, and Jaume Bertranpetti. 2006. The portability of tagSNPs across populations. A Worldwide survey. *Genome research* 13(3):323-30.
- Grant PJ, Humphries SE. 1999. Genetic determinants of arterial thrombosis. *Baillieres Best Pract Res Clin Haematol* 12(3):505-32.
- Green D, Ruth KJ, Folsom AR, Liu K. 1994. Hemostatic factors in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Arterioscler Thromb* 14(5):686-93.
- Green F, Humphries S. 1994. Genetic determinants of arterial thrombosis. *Baillieres Clin Haematol* 7(3):675-92.
- Green F, Kelleher C, Wilkes H, Temple A, Meade T, Humphries S. 1991. A common genetic polymorphism associated with lower coagulation factor VII levels in healthy individuals. *Arterioscler Thromb* 11(3):540-6.
- Greenberg D, Miao CH, Ho WT, Chung DW, Davie EW. 1995. Liver-specific expression of the human factor VII gene. *Proc Natl Acad Sci U S A* 92(26):12347-51.
- Hagen FS, Gray CL, O'Hara P, Grant FJ, Saari GC, Woodbury RG, Hart CE, Insley M, Kisiel W, Kurachi K and others. 1986. Characterization of a cDNA coding for human factor VII. *Proc Natl Acad Sci U S A* 83(8):2412-6.
- Hartl C. 1997. Principles of Population Genetics. Massachusetts: Sinauer Associates.

- Heinrich J, Balleisen L, Schulte H, Assmann G, van de Loo J. 1994. Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. *Arterioscler Thromb* 14(1):54-9.
- Herrmann FH, Wulff K, Auberger K, Aumann V, Bergmann F, Bergmann K, Bratanoff E, Franke D, Grundeis M, Kreuz W and others. 2000. Molecular biology and clinical manifestation of hereditary factor VII deficiency. *Semin Thromb Hemost* 26(4):393-400.
- Hoffman CJ, Miller RH, Hultin MB. 1992. Correlation of factor VII activity and antigen with cholesterol and triglycerides in healthy young adults. *Arterioscler Thromb* 12(3):267-70.
- Hoffman M, Monroe DM, 3rd. 2001. A cell-based model of hemostasis. *Thromb Haemost* 85(6):958-65.
- Hogg PJ, Jackson CM. 1989. Fibrin monomer protects thrombin from inactivation by heparin-antithrombin III: implications for heparin efficacy. *Proc Natl Acad Sci U S A* 86(10):3619-23.
- Hong Y, Pedersen NL, Egberg N, de Faire U. 1999. Genetic effects for plasma factor VII levels independent of and in common with triglycerides. *Thromb Haemost* 81(3):382-6.
- Huang MN, Hung HL, Stanfield-Oakley SA, High KA. 1992. Characterization of the human blood coagulation factor X promoter. *J Biol Chem* 267(22):15440-6.
- Humphries S, Temple A, Lane A, Green F, Cooper J, Miller G. 1996. Low plasma levels of factor VIIc and antigen are more strongly associated with the 10 base pair promoter (-323) insertion than the glutamine 353 variant. *Thromb Haemost* 75(4):567-72.
- Humphries SE, Green FR, Temple A, Dawson S, Henney A, Kelleher CH, Wilkes H, Meade TW, Wiman B, Hamsten A. 1992a. Genetic factors determining thrombosis and fibrinolysis. *Ann Epidemiol* 2(4):371-85.
- Humphries SE, Lane A, Dawson S, Green FR. 1992b. The study of gene-environment interactions that influence thrombosis and fibrinolysis. Genetic variation at the loci for factor VII and plasminogen activator inhibitor-1. *Arch Pathol Lab Med* 116(12):1322-9.

Humphries SE, Lane A, Green FR, Cooper J, Miller GJ. 1994. Factor VII coagulant activity and antigen levels in healthy men are determined by interaction between factor VII genotype and plasma triglyceride concentration. *Arterioscler Thromb* 14(2):193-8.

Hunault M, Arbini AA, Lopaciuk S, Carew JA, Bauer KA. 1997. The Arg353Gln polymorphism reduces the level of coagulation factor VII. In vivo and in vitro studies. *Arterioscler Thromb Vasc Biol* 17(11):2825-9.

Iacoviello L, Di Castelnuovo A, De Knijff P, D'Orazio A, Amore C, Arboretti R, Kluft C, Benedetta Donati M. 1998. Polymorphisms in the coagulation factor VII gene and the risk of myocardial infarction. *N Engl J Med* 338(2):79-85.

Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. 2001. Replication validity of genetic association studies. *Nat Genet* 29(3):306-9

Jackson DA, Symons RH, Berg P. 1972. Biochemical method for inserting new genetic information into DNA of Simian Virus 40: circular SV40 DNA molecules containing lambda phage genes and the galactose operon of Escherichia coli. *Proc Natl Acad Sci U S A* 69(10):2904-9.

Junker R, Heinrich J, Schulte H, van de Loo J, Assmann G. 1997. Coagulation factor VII and the risk of coronary heart disease in healthy men. *Arterioscler Thromb Vasc Biol* 17(8):1539-44.

Kadonaga JT, Tjian R. 1986. Affinity purification of sequence-specific DNA binding proteins. *Proc Natl Acad Sci U S A* 83(16):5889-93.

Kahn M, Kolter R, Thomas C, Figurski D, Meyer R, Remaut E, Helinski DR. 1979. Plasmid cloning vehicles derived from plasmids ColE1, F, R6K, and RK2. *Methods Enzymol* 68:268-80.

Kapiotis S, Jilma B, Pernerstorfer T, Stohlawetz P, Eichler HG, Speiser W. 1998. Plasma levels of activated factor VII decrease during the menstrual cycle. *Thromb Haemost* 80(4):588-91.

Kimura. 1983. The Neutral Theory of Molecular Evolution. Cambridge: Cambridge University Press.

Koeleman BP, Reitsma PH, Allaart CF, Bertina RM. 1994. Activated protein C resistance as an additional risk factor for thrombosis in protein C-deficient families. *Blood* 84(4):1031-5.

- Koster T, Rosendaal FR, Reitsma PH, van der Velden PA, Briet E, Vandebroucke JP. 1994. Factor VII and fibrinogen levels as risk factors for venous thrombosis. A case-control study of plasma levels and DNA polymorphisms--the Leiden Thrombophilia Study (LETS). *Thromb Haemost* 71(6):719-22.
- Kruglyak L. 1999. Prospects for whole-genome linkage disequilibrium mapping of common disease genes. *Nat Genet* 22(2):139-44.
- Kruglyak L, Nickerson DA. 2001. Variation is the spice of life. *Nat Genet* 27(3):234-6.
- Kudaravalli R, Tidd T, Pinotti M, Ratti A, Santacroce R, Margaglione M, Dallapiccola B, Bernardi F, Fortina P, Devoto M and others. 2002. Polymorphic changes in the 5' flanking region of factor VII have a combined effect on promoter strength. *Thromb Haemost* 88(5):763-7.
- Kupfer HG, Hanna BL, Kinne DR. 1960. Congenital factor VII deficiency with normal Stuart activity: clinical, genetic and experimental observations. *Blood* 15:146-63.
- Kurachi K, Kurachi S. 2005. Molecular mechanisms of age-related regulation of genes. *J Thromb Haemost* 3(5):909-14.
- Kurachi S, Deyashiki Y, Takeshita J, Kurachi K. 1999. Genetic mechanisms of age regulation of human blood coagulation factor IX. *Science* 285(5428):739-43.
- Kushner. 1978. An improved method for transformation of Escherichia coli with Col/EI derived plasmids. In: HW. Boyer SN, editor. *Genetic Engineering*. Amsterdam: Elsevier. p 17-23.
- Lander E, Kruglyak L. 1995. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* 11(3):241-7.
- Lane A, Cruickshank JK, Mitchell J, Henderson A, Humphries S, Green F. 1992. Genetic and environmental determinants of factor VII coagulant activity in ethnic groups at differing risk of coronary heart disease. *Atherosclerosis* 94(1):43-50.

- Lane A, Green F, Scarabin PY, Nicaud V, Bara L, Humphries S, Evans A, Luc G, Cambou JP, Arveiler D and others. 1996a. Factor VII Arg/Gln353 polymorphism determines factor VII coagulant activity in patients with myocardial infarction (MI) and control subjects in Belfast and in France but is not a strong indicator of MI risk in the ECTIM study. *Atherosclerosis* 119(1):119-27.
- Lane DA, Grant PJ. 2000. Role of hemostatic gene polymorphisms in venous and arterial thrombotic disease. *Blood* 95(5):1517-32.
- Lane DA, Mannucci PM, Bauer KA, Bertina RM, Bochkov NP, Boulyjenkov V, Chandy M, Dahlback B, Ginter EK, Miletich JP and others. 1996b. Inherited thrombophilia: Part 1. *Thromb Haemost* 76(5):651-62.
- Lane DA, Mannucci PM, Bauer KA, Bertina RM, Bochkov NP, Boulyjenkov V, Chandy M, Dahlback B, Ginter EK, Miletich JP and others. 1996c. Inherited thrombophilia: Part 2. *Thromb Haemost* 76(6):824-34.
- Levin EG, Marzec U, Anderson J, Harker LA. 1984. Thrombin stimulates tissue plasminogen activator release from cultured human endothelial cells. *J Clin Invest* 74(6):1988-95.
- Lewin. 1997. Genes VI. New York: Oxford University Press.
- Lewontin RC. 1964. The Interaction of Selection and Linkage. II. Optimum Models. *Genetics* 50:757-82.
- Leytus SP, Foster DC, Kurachi K, Davie EW. 1986. Gene for human factor X: a blood coagulation factor whose gene organization is essentially identical with that of factor IX and protein C. *Biochemistry* 25(18):5098-102.
- Lijnen HR, Collen D. 1982. Interaction of plasminogen activators and inhibitors with plasminogen and fibrin. *Semin Thromb Hemost* 8(1):2-10.
- Lindqvist PG, Svensson PJ, Dahlback B, Marsal K. 1998. Factor V Q506 mutation (activated protein C resistance) associated with reduced intrapartum blood loss--a possible evolutionary selection mechanism. *Thromb Haemost* 79(1):69-73.

- Lindqvist PG, Zoller B, Dahlback B. 2001. Improved hemoglobin status and reduced menstrual blood loss among female carriers of factor V Leiden--an evolutionary advantage? *Thromb Haemost* 86(4):1122-3.
- Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. 2003. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* 33(2):177-82
- Long GL. 1986. Structure and evolution of the human genes encoding protein C and coagulation factors VII, IX, and X. *Cold Spring Harb Symp Quant Biol* 51 Pt 1:525-9.
- Lowe GD, Rumley A, Woodward M, Morrison CE, Philippou H, Lane DA, Tunstall-Pedoe H. 1997. Epidemiology of coagulation factors, inhibitors and activation markers: the Third Glasgow MONICA Survey. I. Illustrative reference ranges by age, sex and hormone use. *Br J Haematol* 97(4):775-84.
- Macfarlane RG. 1964. An Enzyme Cascade in the Blood Clotting Mechanism, and Its Function as a Biochemical Amplifier. *Nature* 202:498-9.
- Mackman N. 2004. Role of tissue factor in hemostasis, thrombosis, and vascular development. *Arterioscler Thromb Vasc Biol* 24(6):1015-22.
- Mandel M, Higa A. 1970. Calcium-dependent bacteriophage DNA infection. *J Mol Biol* 53(1):159-62.
- Mangel WF, Lin BH, Ramakrishnan V. 1990. Characterization of an extremely large, ligand-induced conformational change in plasminogen. *Science* 248(4951):69-73.
- Marchetti G, Patracchini P, Papacchini M, Ferrati M, Bernardi F. 1993. A polymorphism in the 5' region of coagulation factor VII gene (F7) caused by an inserted decanucleotide. *Hum Genet* 90(5):575-6.
- Mariani G, Herrmann FH, Dolce A, Batorova A, Etro D, Peyvandi F, Wulff K, Schved JF, Auerswald G, Ingerslev J and others. 2005. Clinical phenotypes and factor VII genotype in congenital factor VII deficiency. *Thromb Haemost* 93(3):481-7.

Mateo J, Oliver A, Borrell M, Sala N, Fontcuberta J. 1997. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). *Thromb Haemost* 77(3):444-51.

Mayor C, Brudno M, Schwartz JR, Poliakov A, Rubin EM, Frazer KA, Pachter LS, Dubchak I. 2000. VISTA : visualizing global DNA sequence alignments of arbitrary length. *Bioinformatics* 16(11):1046-7.

McVey JH, Boswell E, Mumford AD, Kemball-Cook G, Tuddenham EG. 2001. Factor VII deficiency and the FVII mutation database. *Hum Mutat* 17(1):3-17.

Meade TW, Mellows S, Brozovic M, Miller GJ, Chakrabarti RR, North WR, Haines AP, Stirling Y, Imeson JD, Thompson SG. 1986. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* 2(8506):533-7.

Meade TW, Ruddock V, Stirling Y, Chakrabarti R, Miller GJ. 1993. Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in the Northwick Park Heart Study. *Lancet* 342(8879):1076-9.

Meilahn E, Ferrell R, Kiss J, Temple A, Green F, Humphries S, Kuller L. 1995. Genetic determination of coagulation factor VIIc levels among healthy middle-aged women. *Thromb Haemost* 73(4):623-5.

Mennen LI, Schouten EG, Grobbee DE, Kluft C. 1996. Coagulation factor VII, dietary fat and blood lipids: a review. *Thromb Haemost* 76(4):492-9.

Miao CH, Leytus SP, Chung DW, Davie EW. 1992. Liver-specific expression of the gene coding for human factor X, a blood coagulation factor. *J Biol Chem* 267(11):7395-401.

Miletich JP, Prescott SM, White R, Majerus PW, Bovill EG. 1993. Inherited predisposition to thrombosis. *Cell* 72(4):477-80.

Miller GJ, Seghatchian MJ, Walter SJ, Howarth DJ, Thompson SG, Esnouf MP, Meade TW. 1986. An association between the factor VII coagulant activity and thrombin activity induced by surface/cold exposure of normal human plasma. *Br J Haematol* 62(2):379-84.

- Miller NE. 1985. Plasma lipoproteins, antihypertensive drugs and coronary heart disease. *J Cardiovasc Pharmacol* 7 Suppl 2:S105-9.
- Miller SA, Dykes DD, Polesky HF. 1988. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res* 16(3):1215.
- Moor E, Silveira A, van't Hooft F, Suontaka AM, Eriksson P, Blomback M, Hamsten A. 1995. Coagulation factor VII mass and activity in young men with myocardial infarction at a young age. Role of plasma lipoproteins and factor VII genotype. *Arterioscler Thromb Vasc Biol* 15(5):655-64.
- Morise H, Shimomura O, Johnson FH, Winant J. 1974. Intermolecular energy transfer in the bioluminescent system of *Aequorea*. *Biochemistry* 13(12):2656-62.
- Morrissey JH, Macik BG, Neuenschwander PF, Comp PC. 1993. Quantitation of activated factor VII levels in plasma using a tissue factor mutant selectively deficient in promoting factor VII activation. *Blood* 81(3):734-44.
- Nakagaki T, Foster DC, Berkner KL, Kisiel W. 1991. Initiation of the extrinsic pathway of blood coagulation: evidence for the tissue factor dependent autoactivation of human coagulation factor VII. *Biochemistry* 30(45):10819-24.
- Noto D, Barbagallo CM, Cefalu AB, Cavera G, Sapienza M, Notarbartolo A, Davi G, Averna MR. 2002. Factor VII activity is an independent predictor of cardiovascular mortality in elderly women of a Sicilian population: results of an 11-year follow-up. *Thromb Haemost* 87(2):206-10.
- O'Hara PJ, Grant FJ, Haldeman BA, Gray CL, Insley MY, Hagen FS, Murray MJ. 1987. Nucleotide sequence of the gene coding for human factor VII, a vitamin K-dependent protein participating in blood coagulation. *Proc Natl Acad Sci U S A* 84(15):5158-62.
- Osterud B, Rapaport SI. 1977. Activation of factor IX by the reaction product of tissue factor and factor VII: additional pathway for initiating blood coagulation. *Proc Natl Acad Sci U S A* 74(12):5260-4.

Palmer LJ, Cardon LR. 2005. Shaking the tree: mapping complex disease genes with linkage disequilibrium. *Lancet* 366(9492):1223-34.

Pan LC, Price PA. 1985. The propeptide of rat bone gamma-carboxyglutamic acid protein shares homology with other vitamin K-dependent protein precursors. *Proc Natl Acad Sci U S A* 82(18):6109-13.

Patil N, Berno AJ, Hinds DA, Barrett WA, Doshi JM, Hacker CR, Kautzer CR, Lee DH, Marjoribanks C, McDonough DP and others. 2001. Blocks of limited haplotype diversity revealed by high-resolution scanning of human chromosome 21. *Science* 294(5547):1719-23.

Pedersen AH, Lund-Hansen T, Bisgaard-Frantzen H, Olsen F, Petersen LC. 1989. Autoactivation of human recombinant coagulation factor VII. *Biochemistry* 28(24):9331-6.

Peyvandi F, Jenkins PV, Mannucci PM, Billio A, Zeinali S, Perkins SJ, Perry DJ. 2000a. Molecular characterisation and three-dimensional structural analysis of mutations in 21 unrelated families with inherited factor VII deficiency. *Thromb Haemost* 84(2):250-7.

Peyvandi F, Mannucci PM, Bucciarelli P, Zeinali S, Akhavan S, Sacchi E, Merlini PA, Perry DJ. 2000b. A novel polymorphism in intron 1a of the human factor VII gene (G73A): study of a healthy Italian population and of 190 young survivors of myocardial infarction. *Br J Haematol* 108(2):247-53.

Pfeiffer RA, Ott R, Gilgenkrantz S, Alexandre P. 1982. Deficiency of coagulation factors VII and X associated with deletion of a chromosome 13 (q34). Evidence from two cases with 46,XY,t(13;Y)(q11;q34). *Hum Genet* 62(4):358-60.

Pinotti M, Toso R, Girelli D, Bindini D, Ferraresi P, Papa ML, Corrocher R, Marchetti G, Bernardi F. 2000. Modulation of factor VII levels by intron 7 polymorphisms: population and in vitro studies. *Blood* 95(11):3423-8.

Pinotti M, Toso R, Redaelli R, Berrettini M, Marchetti G, Bernardi F. 1998. Molecular mechanisms of FVII deficiency: expression of mutations clustered in the IVS7 donor splice site of factor VII gene. *Blood* 92(5):1646-51.

- Plow EF, Collen D. 1981. The presence and release of alpha 2-antiplasmin from human platelets. *Blood* 58(6):1069-74.
- Pollak ES, Hung HL, Godin W, Overton GC, High KA. 1996. Functional characterization of the human factor VII 5'-flanking region. *J Biol Chem* 271(3):1738-47.
- Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. 1996. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 88(10):3698-703.
- Prasher DC, Eckenrode VK, Ward WW, Prendergast FG, Cormier MJ. 1992. Primary structure of the *Aequorea victoria* green-fluorescent protein. *Gene* 111(2):229-33.
- Preissner KT, Machovich R. 2004. Fibrinolysis and proteolysis in a cellular context. *Thromb Haemost* 91(3):423-4.
- Pugh BF, Tjian R. 1990. Mechanism of transcriptional activation by Sp1: evidence for coactivators. *Cell* 61(7):1187-97.
- Pytela R, Pierschbacher MD, Ginsberg MH, Plow EF, Ruoslahti E. 1986. Platelet membrane glycoprotein IIb/IIIa: member of a family of Arg-Gly-Asp--specific adhesion receptors. *Science* 231(4745):1559-62.
- Radcliffe R, Nemerson Y. 1975. Activation and control of factor VII by activated factor X and thrombin. Isolation and characterization of a single chain form of factor VII. *J Biol Chem* 250(2):388-95.
- Rao LV, Rapaport SI. 1987. Studies of a mechanism inhibiting the initiation of the extrinsic pathway of coagulation. *Blood* 69(2):645-51.
- Rao LV, Rapaport SI. 1988. Activation of factor VII bound to tissue factor: a key early step in the tissue factor pathway of blood coagulation. *Proc Natl Acad Sci U S A* 85(18):6687-91.
- Rao P. 2001. Genetic Dissection of Complex Traits: Academic Press.

Reich DE, Cargill M, Bolk S, Ireland J, Sabeti PC, Richter DJ, Lavery T, Kouyoumjian R, Farhadian SF, Ward R and others. 2001. Linkage disequilibrium in the human genome. *Nature* 411(6834):199-204.

Reich DE, Lander ES. 2001. On the allelic spectrum of human disease. *Trends Genet* 17(9):502-10.

Reijnen MJ, Sladek FM, Bertina RM, Reitsma PH. 1992. Disruption of a binding site for hepatocyte nuclear factor 4 results in hemophilia B Leyden. *Proc Natl Acad Sci U S A* 89(14):6300-3.

Risch N, Merikangas K. 1996. The future of genetic studies of complex human diseases. *Science* 273(5281):1516-7.

Rogers J, Mahaney MC, Almasy L, Comuzzie AG, Blangero J. 1999. Quantitative trait linkage mapping in anthropology. *Am J Phys Anthropol Suppl* 29:127-51.

Rosen ED, Chan JC, Idusogie E, Clotman F, Vlasuk G, Luther T, Jalbert LR, Albrecht S, Zhong L, Lissens A and others. 1997. Mice lacking factor VII develop normally but suffer fatal perinatal bleeding. *Nature* 390(6657):290-4.

Rosendaal FR. 1999. Venous thrombosis: a multicausal disease. *Lancet* 353(9159):1167-73.

Rozas J, Rozas R. 1999. DnaSP version 3: an integrated program for molecular population genetics and molecular evolution analysis. *Bioinformatics* 15(2):174-5.

Ruggeri ZM. 2003. Von Willebrand factor, platelets and endothelial cell interactions. *J Thromb Haemost* 1(7):1335-42.

Sachidanandam R, Weissman D, Schmidt SC, Kakol JM, Stein LD, Marth G, Sherry S, Mullikin JC, Mortimore BJ, Willey DL and others. 2001. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 409(6822):928-33.

Saiki RK, Gelfand DH, Stoffel S, Scharf SJ, Higuchi R, Horn GT, Mullis KB, Erlich HA. 1988. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 239(4839):487-91.

- Sakkinen PA, Cushman M, Psaty BM, Kuller LH, Bajaj SP, Sabharwal AK, Boineau R, Macy E, Tracy RP. 1998. Correlates of antithrombin, protein C, protein S, and TFPI in a healthy elderly cohort. *Thromb Haemost* 80(1):134-9.
- Sambrook R. 2001. Molecular Cloning: A Laboratory Manual. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press.
- Sanger F, Nicklen S, Coulson AR. 1977. DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U S A* 74(12):5463-7.
- Scarabin PY, Bara L, Samama M, Orssaud G. 1985. Further evidence that activated factor VII is related to plasma lipids. *Br J Haematol* 61(1):186-7.
- Scarabin PY, Van Dreden P, Bonithon-Kop C, Orssaud G, Bara L, Conard J, Samama M. 1988. Age-related changes in factor VII activation in healthy women. *Clin Sci (Lond)* 75(4):341-3.
- Schwartz ML, Pizzo SV, Hill RL, McKee PA. 1973. Human Factor XIII from plasma and platelets. Molecular weights, subunit structures, proteolytic activation, and cross-linking of fibrinogen and fibrin. *J Biol Chem* 248(4):1395-407.
- Selander-Sunnerhagen M, Ullner M, Persson E, Teleman O, Stenflo J, Drakenberg T. 1992. How an epidermal growth factor (EGF)-like domain binds calcium. High resolution NMR structure of the calcium form of the NH₂-terminal EGF-like domain in coagulation factor X. *J Biol Chem* 267(27):19642-9.
- Shamsher MK, Chuzhanova NA, Friedman B, Scopes DA, Alhaq A, Millar DS, Cooper DN, Berg LP. 2000. Identification of an intronic regulatory element in the human protein C (PROC) gene. *Hum Genet* 107(5):458-65.
- Shigekawa K, Dower WJ. 1988. Electroporation of eukaryotes and prokaryotes: a general approach to the introduction of macromolecules into cells. *Biotechniques* 6(8):742-51.
- Sidelmann JJ, Gram J, Jespersen J, Kluft C. 2000. Fibrin clot formation and lysis: basic mechanisms. *Semin Thromb Hemost* 26(6):605-18.

Sladek FM, Zhong WM, Lai E, Darnell JE, Jr. 1990. Liver-enriched transcription factor HNF-4 is a novel member of the steroid hormone receptor superfamily. *Genes Dev* 4(12B):2353-65.

Smith DJ, Lusis AJ. 2002. The allelic structure of common disease. *Hum Mol Genet* 11(20):2455-61.

Smith FB, Lee AJ, Fowkes FG, Price JF, Rumley A, Lowe GD. 1997. Hemostatic factors as predictors of ischemic heart disease and stroke in the Edinburgh Artery Study. *Arterioscler Thromb Vasc Biol* 17(11):3321-5.

Souto JC. 2003. Genetic studies in complex disease: the case pro linkage studies. *J Thromb Haemost* 1(8):1676-8.

Souto JC, Almasy L, Blangero J, Stone W, Borrell M, Urrutia T, Mateo J, Fontcuberta J. 2001. Genetic regulation of plasma levels of vitamin K-dependent proteins involved in hemostasis: results from the GAIT Project. Genetic Analysis of Idiopathic Thrombophilia. *Thromb Haemost* 85(1):88-92.

Souto JC, Almasy L, Borrell M, Blanco-Vaca F, Mateo J, Soria JM, Coll I, Felices R, Stone W, Fontcuberta J and others. 2000a. Genetic susceptibility to thrombosis and its relationship to physiological risk factors: the GAIT study. Genetic Analysis of Idiopathic Thrombophilia. *Am J Hum Genet* 67(6):1452-9.

Souto JC, Almasy L, Borrell M, Gari M, Martinez E, Mateo J, Stone WH, Blangero J, Fontcuberta J. 2000b. Genetic determinants of hemostasis phenotypes in Spanish families. *Circulation* 101(13):1546-51.

Souto JC, Almasy L, Borrell M, Stone WH, Blanco-Vaca F, Soria JM, Blangero J, Fontcuberta J. 2002. Thromboplastin-thrombomodulin-mediated time and serum folate levels are genetically correlated with the risk of thromboembolic disease: results from the GAIT project. *Thromb Haemost* 87(1):68-73.

Souto JC, Coll I, Llobet D, del Rio E, Oliver A, Mateo J, Borrell M, Fontcuberta J. 1998. The prothrombin 20210A allele is the most prevalent genetic risk factor for venous thromboembolism in the Spanish population. *Thromb Haemost* 80(3):366-9.

- Spronk HM, Govers-Riemslag JW, ten Cate H. 2003. The blood coagulation system as a molecular machine. *Bioessays* 25(12):1220-8.
- Stearns-Kurosawa DJ, Kurosawa S, Mollica JS, Ferrell GL, Esmon CT. 1996. The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex. *Proc Natl Acad Sci U S A* 93(19):10212-6.
- Strachan R. 1999. Human Molecular Genetics 2. Oxford: BIOS Scientific Publishers.
- Stumpf MP. 2002. Haplotype diversity and the block structure of linkage disequilibrium. *Trends Genet* 18(5):226-8.
- The International HapMap Consortium. 2003. The International HapMap Project. *Nature* 426(6968):789-96.
- Tirado I, Mateo J, Soria JM, Oliver A, Borrell M, Coll I, Vallve C, Souto JC, Martinez-Sanchez E, Fontcuberta J. 2001. Contribution of prothrombin 20210A allele and factor V Leiden mutation to thrombosis risk in thrombophilic families with other hemostatic deficiencies. *Haematologica* 86(11):1200-8.
- Toso R, Pinotti M, High KA, Pollak ES, Bernardi F. 2002. A frequent human coagulation Factor VII mutation (A294V, c152) in loop 140s affects the interaction with activators, tissue factor and substrates. *Biochem J* 363(Pt 2):411-6.
- Triplett DA, Brandt JT, Batard MA, Dixon JL, Fair DS. 1985. Hereditary factor VII deficiency: heterogeneity defined by combined functional and immunochemical analysis. *Blood* 66(6):1284-7.
- Tuddenham C. 1994. The molecular genetics of haemostasis and its inherited disorders. Oxford: Oxford University Press.
- van Boven HH, Lane DA. 1997. Antithrombin and its inherited deficiency states. *Semin Hematol* 34(3):188-204.

van 't Hooft FM, Silveira A, Tornvall P, Iliadou A, Ehrenborg E, Eriksson P, Hamsten A. 1999. Two common functional polymorphisms in the promoter region of the coagulation factor VII gene determining plasma factor VII activity and mass concentration. *Blood* 93(10):3432-41.

Virchow R. 1860. Cellular pathology. London: Churchill.

Voetsch B, Loscalzo J. 2004. Genetic determinants of arterial thrombosis. *Arterioscler Thromb Vasc Biol* 24(2):216-29.

Wang XL, Wang J, McCredie RM, Wilcken DE. 1997. Polymorphisms of factor V, factor VII, and fibrinogen genes. Relevance to severity of coronary artery disease. *Arterioscler Thromb Vasc Biol* 17(2):246-51.

Weiss HJ, Turitto VT. 1979. Prostacyclin (prostaglandin I₂, PGI₂) inhibits platelet adhesion and thrombus formation on subendothelium. *Blood* 53(2):244-50.

Weiss K. 1993a. Genetic Variation and Human Disease. Principles and evolutionary approaches. Cambridge: Cambridge University Press.

Weiss KB. 1993b. Inappropriate statistics. *Pediatrics* 91(2):517-8.

Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. 1990. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 86(2):385-91.

Wildgoose P, Nemerson Y, Hansen LL, Nielsen FE, Glazer S, Hedner U. 1992. Measurement of basal levels of factor VIIa in hemophilia A and B patients. *Blood* 80(1):25-8.

Williams JT, Begleiter H, Porjesz B, Edenberg HJ, Foroud T, Reich T, Goate A, Van Eerdewegh P, Almasy L, Blangero J. 1999. Joint multipoint linkage analysis of multivariate qualitative and quantitative traits. II. Alcoholism and event-related potentials. *Am J Hum Genet* 65(4):1148-60.

Williams JT, Blangero J. 1999. Comparison of variance components and sibpair-based approaches to quantitative trait linkage analysis in unselected samples. *Genet Epidemiol* 16(2):113-34.

- Wilson JF, Goldstein DB. 2000. Consistent long-range linkage disequilibrium generated by admixture in a Bantu-Semitic hybrid population. *Am J Hum Genet* 67(4):926-35.
- Wulff K, Herrmann FH. 2000. Twenty two novel mutations of the factor VII gene in factor VII deficiency. *Hum Mutat* 15(6):489-96.
- Zaykin DV, Zhivotovsky LA. 2005. Ranks of genuine associations in whole-genome scans. *Genetics* 171(2):813-23.
- Zheng DQ, Shurafa M, James HL. 1996. Factor VII G331D: a variant molecule involving replacement of a residue in the substrate-binding region of the catalytic domain. *Blood Coagul Fibrinolysis* 7(1):93-6.
- Zoller B, Berntsdotter A, Garcia de Frutos P, Dahlback B. 1995. Resistance to activated protein C as an additional genetic risk factor in hereditary deficiency of protein S. *Blood* 85(12):3518-23.
- Zoller B, Garcia de Frutos P, Hillarp A, Dahlback B. 1999. Thrombophilia as a multigenic disease. *Haematologica* 84(1):59-70.
- Zwaal RF. 1978. Membrane and lipid involvement in blood coagulation. *Biochim Biophys Acta* 515(2):163-205.