Genetic variation and susceptibility to venous thrombosis : Etiology and risk assessment

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References

REFERENCES

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerström J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007; 5(4):692-699.

2. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003; 107(23 Suppl 1):I4-I8.

3. Chinthammitr Y, Vos HL, Rosendaal FR, Doggen CJM. The association of prothrombin A19911G polymorphism with plasma prothrombin activity and venous thrombosis: results of the MEGA study, a large population-based case-control study. *J Thromb Haemost* 2006; 4(12):2587-2592.

4. Virchow R.L.K. Gesammelte Abhandlungen zur Wissenschaftlichen Medicin. *Frankfurt, Meidinger Sohn & Co* 1856.

5. Dickson BC. Venous Thrombosis: On the History of Virchow's Triad. *Univ Toronto Med J* 2004; 81(3):166-171.

6. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999; 353(9159):1167-1173.

7. Nossent AY, Eikenboom JC, Bertina RM. Plasma coagulation factor levels in venous thrombosis. *Semin Hematol* 2007; 44(2):77-84.

8. The International HapMap Project. *Nature* 2003; 426(6968):789-796.

9. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; 447(7145):661-678.

10. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 2007; 316(5829):1341-1345.

11. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 2007; 445(7130):881-885.

12. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 2007; 447(7148):1087-1093.

13. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet* 2007; 39(7):870-874.

14. Gold B, Kirchhoff T, Stefanov S, Lautenberger J, Viale A, Garber J et al. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. *Proc Natl Acad Sci U S A* 2008; 105(11):4340-4345.

15. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 2005; 6(2):95-108.

16. Kruglyak L, Nickerson DA. Variation is the spice of life. *Nat Genet* 2001; 27(3):234-236.

17. Koster T, Rosendaal FR, De Ronde H, Briët E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. *Lancet* 1993; 342(8886-8887):1503-1506.

18. van der Meer FJM, Koster T, Vandenbroucke JP, Briët E, Rosendaal FR. The Leiden Thrombophilia Study (LETS). *Thromb Haemost* 1997; 78(1):631-635.

19. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA* 2005; 293(6):715-722.

20. van Stralen KJ, Rosendaal FR, Doggen CJM. Minor injuries as a risk factor for venous thrombosis. *Arch Intern Med* 2008; 168(1):21-26.

21. Miller GJ, Bauer KA, Barzegar S, Cooper JA, Rosenberg RD. Increased activation of the haemostatic system in men at high risk of fatal coronary heart disease. *Thromb Haemost* 1996; 75(5):767-771.

22. Vandenbroucke JP, Koster T, Briët E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet* 1994; 344(8935):1453-1457.

23. Vandenbroucke JP, van der Meer FJM, Helmerhorst FM, Rosendaal FR. Factor V Leiden: should we screen oral contraceptive users and pregnant women? *BMJ* 1996; 313(7065): 1127-1130.

24. Wu O, Robertson L, Twaddle S, Lowe G, Clark P, Walker I et al. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. *Br J Haematol* 2005; 131(1):80-90.

25. Briët E, van der Meer FJM, Rosendaal FR, Houwing-Duistermaat JJ, van Houwelingen HC. The family history and inherited thrombophilia. *Br J Haematol* 1994; 87(2):348-352.

26. Cosmi B, Legnani C, Bernardi F, Coccheri S, Palareti G. Value of family history in identifying women at risk of venous thromboembolism during oral contraception: observational study. *BMJ* 2001; 322(7293):1024-1025.

27. Aznar J, Mira Y, Vaya A, Ferrando F, Villa P. Is family history sufficient to identify women with risk of venous thromboembolism before commencing the contraceptive pill? *Clin Appl Thromb Hemost* 2002; 8(2):139-141.

28. Caprini JA, Goldshteyn S, Glase CJ, Hathaway K. Thrombophilia testing in patients with venous thrombosis. *Eur J Vasc Endovasc Surg* 2005; 30(5):550-555.

29. van Sluis GL, Söhne M, El Kheir DY, Tanck MW, Gerdes VEA, Büller HR. Family history and inherited thrombophilia. *J Thromb Haemost* 2006; 4(10):2182-2187.

30. Dowling NF, Austin H, Dilley A, Whitsett C, Evatt BL, Hooper WC. The epidemiology of venous thromboembolism in Caucasians and African-Americans: the GATE Study. *J Thromb Haemost* 2003; 1(1):80-87.

31. Noboa S, Le Gal G, Lacut K, Mercier B, Leroyer C, Nowak E et al. Family history as a risk factor for venous thromboembolism. *Thromb Res* 2008.

32. Pomp ER, le CS, Rosendaal FR, Doggen CJM. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. *Br J Haematol* 2007; 139(2):289-296.

33. Waksberg J. Sampling methods for Random Digit Dialing. *J Am Stat Assoc* 1978; 73:40-46.

34. O'Brien AE, Tate GM, Shiach C. Evaluation of protein C and protein S levels during oral anticoagulant therapy. *Clin Lab Haematol* 1998; 20(4):245-252.

35. Cosmi B, Legnani C, Bernardi F, Coccheri S, Palareti G. Role of family history in identifying women with thrombophilia and higher risk of venous thromboembolism during oral contraception. *Arch Intern Med* 2003; 163(9):1105-1109.

36. Miletich J, Sherman L, Broze G, Jr. Absence of thrombosis in subjects with heterozygous protein C deficiency. *N Engl J Med* 1987; 317(16):991-996.

37. Anton-Culver H, Kurosaki T, Taylor TH, Gildea M, Brunner D, Bringman D. Validation of family history of breast cancer and identification of the BRCA1 and other syndromes using a population-based cancer registry. *Genet Epidemiol* 1996; 13(2):193-205.

38. Louis ED, Ford B, Wendt KJ, Ottman R. Validity of family history data on essential tremor. *Mov Disord* 1999; 14(3):456-461.

39. Ziogas A, Anton-Culver H. Validation of family history data in cancer family registries. *Am J Prev Med* 2003; 24(2):190-198.

40. Elbaz A, McDonnell SK, Maraganore DM, Strain KJ, Schaid DJ, Bower JH et al. Validity of family history data on PD: evidence for a family information bias. *Neurology* 2003; 61(1):11-17.

41. Mitchell RJ, Brewster D, Campbell H, Porteous ME, Wyllie AH, Bird CC et al. Accuracy of reporting of family history of colorectal cancer. *Gut* 2004; 53(2):291-295.

42. Koster T, Rosendaal FR, Briët E, van der Meer FJM, Colly LP, Trienekens PH et al. Protein C deficiency in a controlled series of unselected outpatients: an infrequent but clear risk factor for venous thrombosis (Leiden Thrombophilia Study). *Blood* 1995; 85(10):2756-2761.

43. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003; 362(9383):523-526.

44. Hron G, Eichinger S, Weltermann A, Minar E, Bialonczyk C, Hirschl M et al. Family history for venous thromboembolism and the risk for recurrence. *Am J Med* 2006; 119(1):50-53.

45. Mannucci PM. Laboratory detection of inherited thrombophilia: a historical perspective. *Semin Thromb Hemost* 2005; 31(1):5-10.

46. Koster T, Rosendaal FR, Reitsma PH, van der Velden PA, Briët E, Vandenbroucke JP. 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* 1994; 71(6):719-722.

47. Austin H, Hooper WC, Lally C, Dilley A, Ellingsen D, Wideman C et al. Venous thrombosis in relation to fibrinogen and factor VII genes among African-Americans. *J Clin Epidemiol* 2000; 53(10):997-1001.

48. Carter AM, Catto AJ, Kohler HP, Ariens RA, Stickland MH, Grant PJ. alpha-fibrinogen Thr312Ala polymorphism and venous thromboembolism. *Blood* 2000; 96(3):1177-1179.

49. Ko YL, Hsu LA, Hsu TS, Tsai CT, Teng MS, Wu S et al. Functional polymorphisms of FGA, encoding alpha fibrinogen, are associated with susceptibility to venous thromboembolism in a Taiwanese population. *Hum Genet* 2006; 119(1-2):84-91.

50. Uitte dW, de Visser MCH, Houwing-Duistermaat JJ, Rosendaal FR, Vos HL, Bertina RM. Genetic variation in the fibrinogen gamma gene increases the risk for deep venous thrombosis by reducing plasma fibrinogen gamma' levels. *Blood* 2005; 106(13): 4176-4183.

51. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. 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* 1996; 88(10):3698-3703.

52. Ceelie H, Spaargaren-Van Riel CC, Lyon E, Bertina RM, Vos HL. Functional analysis of two polymorphisms in the 3'-UTR of the human prothrombin gene. *J Thromb Haemost* 2005; 3(4):806-808.

53. Ceelie H, Bertina RM, van Hylckama Vlieg A, Rosendaal FR, Vos HL. Polymorphisms in the prothrombin gene and their association with plasma prothrombin levels. *Thromb Haemost* 2001; 85(6):1066-1070.

54. Martinelli I, Battaglioli T, Tosetto A, Legnani C, Sottile L, Ghiotto R et al. Prothrombin A19911G polymorphism and the risk of venous thromboembolism. *J Thromb Haemost* 2006; 4(12):2582-2586.

55. Perez-Ceballos E, Corral J, Alberca I, Vaya A, Llamas P, Montes R et al. Prothrombin A19911G and G20210A polymorphisms' role in thrombosis. *Br J Haematol* 2002; 118(2):610-614.

56. Castaman G, Faioni EM, Tosetto A, Bernardi F. The factor V HR2 haplotype and the risk of venous thrombosis: a meta-analysis. *Haematologica* 2003; 88(10):1182-1189.

57. Scanavini D, Legnani C, Lunghi B, Mingozzi F, Palareti G, Bernardi F. The factor VIII D1241E polymorphism is associated with decreased factor VIII activity and not with activated protein C resistance levels. *Thromb Haemost* 2005; 93(3):453-456.

58. Nossent AY, Eikenboom JCJ, Vos HL, Bakker E, Tanis BC, Doggen CJM et al. Haplotypes encoding the factor VIII 1241 Glu variation, factor VIII levels and the risk of venous thrombosis. *Thromb Haemost* 2006; 95(6):942-948.

59. Wells PS, Anderson JL, Scarvelis DK, Doucette SP, Gagnon F. Factor XIII Val34Leu variant is protective against venous thromboembolism: a HuGE review and meta-analysis. *Am J Epidemiol* 2006; 164(2):101-109.

60. Komanasin N, Catto AJ, Futers TS, van Hylckama Vlieg A, Rosendaal FR, Ariens RA. A novel polymorphism in the factor XIII B-subunit (His95Arg): relationship to subunit dissociation and venous thrombosis. *J Thromb Haemost* 2005; 3(11):2487-2496.

61. Arnaud E, Barbalat V, Nicaud V, Cambien F, Evans A, Morrison C et al. Polymorphisms in the 5' regulatory region of the tissue factor gene and the risk of myocardial infarction and venous thromboembolism: the ECTIM and PATHROS studies. Etude Cas-Temoins de l'Infarctus du Myocarde. Paris Thrombosis case-control Study. *Arterioscler Thromb Vasc Biol* 2000; 20(3):892-898.

62. Buddingh EP, van Hylckama Vlieg A, Rosendaal FR. The angiotensin-converting enzyme gene insertion/deletion polymorphism: insufficient evidence for a role in deep venous thrombosis. *J Thromb Haemost* 2005; 3(2):403-404.

63. Kleesiek K, Schmidt M, Gotting C, Schwenz B, Lange S, Muller-Berghaus G et al. The 536C-->T transition in the human tissue factor pathway inhibitor (TFPI) gene is statistically associated with a higher risk for venous thrombosis. *Thromb Haemost* 1999; 82(1):1-5.

64. Ameziane N, Seguin C, Borgel D, Fumeron F, Moatti D, Alhenc-Gelas M et al. The -33T-->C polymorphism in intron 7 of the TFPI gene influences the risk of venous thromboembolism, independently of the factor V Leiden and prothrombin mutations. *Thromb Haemost* 2002; 88(2):195-199.

65. Barcellona D, Fenu L, Cauli C, Pisu G, Marongiu F. Allele 4G of gene PAI-1 associated with prothrombin mutation G20210A increases the risk for venous thrombosis. *Thromb Haemost* 2003; 90(6):1061-1064.

66. Morelli VM, de Visser MCH, Vos HL, Bertina RM, Rosendaal FR. ABO blood group genotypes and the risk of venous thrombosis: effect of factor V Leiden. *J Thromb Haemost* 2005; 3(1):183-185.

67. Razzari C, Martinelli I, Bucciarelli P, Viscardi Y, Biguzzi E. Polymorphisms of the protein Z-dependent protease inhibitor (ZPI) gene and the risk of venous thromboembolism. *Thromb Haemost* 2006; 95(5):909-910.

68. Vos HL. Inherited defects of coagulation Factor V: the thrombotic side. *J Thromb Haemost* 2006; 4(1):35-40.

69. Lunghi B, Iacoviello L, Gemmati D, Dilasio MG, Castoldi E, Pinotti M et al. Detection of new polymorphic markers in the factor V gene: association with factor V levels in plasma. *Thromb Haemost* 1996; 75(1):45-48.

70. Roelse JC, Koopman MM, Buller HR, ten Cate JW, Montaruli B, van Mourik JA et al. Absence of mutations at the activated protein C cleavage sites of factor VIII in 125 patients with venous thrombosis. *Br J Haematol* 1996; 92(3):740-743.

71. Mansvelt EP, Laffan M, McVey JH, Tuddenham EG. Analysis of the F8 gene in individuals with high plasma factor VIII: C levels and associated venous thrombosis. *Thromb Haemost* 1998; 80(4):561-565.

72. Kamphuisen PW, Eikenboom JCJ, Rosendaal FR, Koster T, Blann AD, Vos HL et al. High factor VIII antigen levels increase the risk of venous thrombosis but are not associated with polymorphisms in the von Willebrand factor and factor VIII gene. *Br J Haematol* 2001; 115(1):156-158.

73. Machiah D, Viel K, Almasy L, Soria JM, Porter S, Souto JC et al. A common SNP in the factor VIII (f-VIII) gene encodes a conservative aspartate to glutamate substitution (Asp1241 Glu) in the B-domain that influences f-VIII activity levels. *Blood* 2003; 102(11).

74. Kanaji T, Okamura T, Osaki K, Kuroiwa M, Shimoda K, Hamasaki N et al. A common genetic polymorphism (46 C to T substitution) in the 5'-untranslated region of the coagulation factor XII gene is associated with low translation efficiency and decrease in plasma factor XII level. *Blood* 1998; 91(6):2010-2014.

75. Tirado I, Soria JM, Mateo J, Oliver A, Souto JC, Santamaria A et al. Association after linkage analysis indicates that homozygosity for the 46C-->T polymorphism in the F12 gene is a genetic risk factor for venous thrombosis. *Thromb Haemost* 2004; 91(5):899-904.

76. Franco RF, Reitsma PH, Lourenco D, Maffei FH, Morelli V, Tavella MH et al. Factor XIII Val34Leu is a genetic factor involved in the etiology of venous thrombosis. *Thromb Haemost* 1999; 81(5):676-679.

77. Bertina RM, Poort SR, Vos HL, Rosendaal FR. The 46C-->T polymorphism in the factor XII gene (F12) and the risk of venous thrombosis. *J Thromb Haemost* 2005; 3(3):597-599.

78. Grunbacher G, Marx-Neuhold E, Pilger E, Koppel H, Renner W. The functional -4C>T polymorphism of the coagulation factor XII gene is not associated with deep venous thrombosis. *J Thromb Haemost* 2005; 3(12):2815-2817.

79. Ariens RA, Philippou H, Nagaswami C, Weisel JW, Lane DA, Grant PJ. The factor XIII V34L polymorphism accelerates thrombin activation of factor XIII and affects cross-linked fibrin structure. *Blood* 2000; 96(3):988-995.

80. Catto AJ, Kohler HP, Coore J, Mansfield MW, Stickland MH, Grant PJ. Association of a common polymorphism in the factor XIII gene with venous thrombosis. *Blood* 1999; 93(3):906-908.

81. Wells PS, Anderson JL, Rodger MA, Carson N, Grimwood RL, Doucette SP. The factor XIII Val34Leu polymorphism: is it protective against idiopathic venous thromboembolism? *Blood Coagul Fibrinolysis* 2006; 17(7):533-538.

82. Vossen CY, Rosendaal FR. The protective effect of the factor XIII Val34Leu mutation on the risk of deep venous thrombosis is dependent on the fibrinogen level. *J Thromb Haemost* 2005; 3(5):1102-1103.

83. Zawadzki C, Preudhomme C, Gaveriaux V, Amouyel P, Jude B. The Arg200Trp mutation in the human tissue factor gene. *Thromb Haemost* 2002; 87(3):540-541.

84. Roemisch J, Feussner A, Nerlich C, Stoehr HA, Weimer T. The frequent Marburg I polymorphism impairs the pro-urokinase activating potency of the factor VII activating protease (FSAP). *Blood Coagul Fibrinolysis* 2002; 13(5):433-441.

85. Hoppe B, Tolou F, Radtke H, Kiesewetter H, Dorner T, Salama A. Marburg I polymorphism of factor VII-activating protease is associated with idiopathic venous thromboembolism. *Blood* 2005; 105(4):1549-1551.

86. van Minkelen R, de Visser MCH, Vos HL, Bertina RM, Rosendaal FR. The Marburg I polymorphism of factor VII-activating protease is not associated with venous thrombosis. *Blood* 2005; 105(12):4898.

87. Franchi F, Martinelli I, Biguzzi E, Bucciarelli P, Mannucci PM. Marburg I polymorphism of factor VII-activating protease and risk of venous thromboembolism. *Blood* 2006; 107(4):1731.

88. Jick H, Slone D, Westerholm B, Inman WH, Vessey MP, Shapiro S et al. Venous thromboembolic disease and ABO blood type. A cooperative study. *Lancet* 1969; 1(7594):539-542.

89. Koster T, Blann AD, Briët E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* 1995; 345(8943):152-155.

90. Mercier B, Oger E, Le Gal G, Mottier D, Ferec C. Phenotypic but not allelic ABO blood group association with risk of venous thrombosis. *Thromb Haemost* 2005; 93(2):388-389.

91. Schleef M, Strobel E, Dick A, Frank J, Schramm W, Spannagl M. Relationship between ABO and Secretor genotype with plasma levels of factor VIII and von Willebrand factor in thrombosis patients and control individuals. *Br J Haematol* 2005; 128(1):100-107.

92. Tirado I, Mateo J, Soria JM, Oliver A, Martinez-Sanchez E, Vallve C et al. The ABO blood group genotype and factor VIII levels as independent risk factors for venous thromboembolism. *Thromb Haemost* 2005; 93(3):468-474.

93. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990; 86(4):1343-1346.

94. Dilley A, Austin H, Hooper WC, Lally C, Ribeiro MJ, Wenger NK et al. Relation of three genetic traits to venous thrombosis in an African-American population. *Am J Epidemiol* 1998; 147(1):30-35.

95. Philipp CS, Dilley A, Saidi P, Evatt B, Austin H, Zawadsky J et al. Deletion polymorphism in the angiotensin-converting enzyme gene as a thrombophilic risk factor after hip arthroplasty. *Thromb Haemost* 1998; 80(6):869-873.

96. Okumus G, Arseven O. Insertion/deletion polymorphism of the angiotensin-converting enzyme gene: really a risk factor for venous thromboembolism? *Thromb Haemost* 2003; 90(5):766-767.

97. Ekim N, Oguzulgen IK, Demir N, Altinok B, Akar N. The role of angiotensin-converting enzyme gene polymorphism in pulmonary thromboembolism. *Thromb Haemost* 2004; 92(2):432-433.

98. Amini-Nekoo A, Futers TS, Moia M, Mannucci PM, Grant PJ, Ariens RA. Analysis of the tissue factor pathway inhibitor gene and antigen levels in relation to venous thrombosis. *Br J Haematol* 2001; 113(2):537-543.

99. Miyata T, Sakata T, Kumeda K, Uchida K, Tsushima M, Fujimura H et al. C-399T polymorphism in the promoter region of human tissue factor pathway inhibitor (TFPI) gene does not change the plasma TFPI antigen level and does not cause venous thrombosis. *Thromb Haemost* 1998; 80(2):345-346.

100. Gonzalez-Conejero R, Lozano ML, Corral J, Martinez C, Vicente V. The TFPI 536C [right arrow]T mutation is not associated with increased risk for venous or arterial thrombosis. *Thromb Haemost* 2000; 83(5):787-788.

101. Hessner MJ, Luhm RA. The C536T transition in the tissue factor pathway inhibitor (TFPI) gene does not contribute to risk of venous thrombosis among carriers of factor V Leiden. *Thromb Haemost* 2000; 84(4):724-725.

102. Paciaroni K, Rossi E, Bazzan M, Ireland H, De Stefano V. Prevalence of the C536T mutation in the tissue factor pathway inhibitor (TFPI) gene among patients with venous thromboembolic disease. *Thromb Haemost* 2001; 85(5):938-939.

103. Moatti D, Seknadji P, Galand C, Poirier O, Fumeron F, Desprez S et al. Polymorphisms of the tissue factor pathway inhibitor (TFPI) gene in patients with acute coronary syndromes and in healthy subjects : impact of the V264M substitution on plasma levels of TFPI. *Arterioscler Thromb Vasc Biol* 1999; 19(4):862-869.

104. Moatti D, Haidar B, Fumeron F, Gauci L, Boudvillain O, Seknadji P et al. A new T-287C polymorphism in the 5' regulatory region of the tissue factor pathway inhibitor gene. Association study of the T-287C and C-399T polymorphisms with coronary artery disease and plasma TFPI levels. *Thromb Haemost* 2000; 84(2):244-249.

105. Arnaud E, Moatti D, Emmerich J, Aiach M, de Prost D. No link between the TFPI V264M mutation and venous thromboembolic disease. *Thromb Haemost* 1999; 82(1):159-160.

106. Uitte dW, Van M, V, Rosendaal FR, Vos HL, de Visser MCH, Bertina RM. Haplotypes of the EPCR gene, plasma sEPCR levels and the risk of deep venous thrombosis. *J Thromb Haemost* 2004; 2(8):1305-1310.

107. Biguzzi E, Merati G, Liaw PC, Bucciarelli P, Oganesyan N, Qu D et al. A 23bp insertion in the endothelial protein C receptor (EPCR) gene impairs EPCR function. *Thromb Haemost* 2001; 86(4):945-948.

108. Biguzzi E, Gu JM, Merati G, Esmon NL, Esmon CT. Point mutations in the endothelial protein C receptor (EPCR) promoter. *Thromb Haemost* 2002; 87(6):1085-1086.

109. Grossmann R, Schwender S, Geisen U, Schambeck C, Merati G, Walter U. CBS 844ins68, MTHFR TT677 and EPCR 4031ins23 genotypes in patients with deep-vein thrombosis. *Thromb Res* 2002; 107(1-2):13-15.

110. Poort SR, Vos HL, Rosendaal FR, Bertina RM. The endothelial protein C receptor (EPCR) 23 bp insert mutation and the risk of venous thrombosis. *Thromb Haemost* 2002; 88(1): 160-162.

111. von Depka M, Czwalinna A, Eisert R, Wermes C, Scharrer I, Ganser A et al. Prevalence of a 23bp insertion in exon 3 of the endothelial cell protein C receptor gene in venous thrombophilia. *Thromb Haemost* 2001; 86(6):1360-1362.

112. Espana F. A new polymorphism in the 3'UTR region of the endothelias protein C receptor associated with increased levels of circulating activated protein c and decreased risk of venous thrombosis. *Thromb Haemost* 2001; 1:885.

113. Galligan L, Powell C, Livingstone W, Mynett-Johnston L, Smith OP. The G7763C endothelial protein C receptor (EPCR) gene mutation: prevalence and association with DVT in the Irish population. *Thromb Haemost* 2002; 88(1):163-165.

114. Medina P, Navarro S, Estelles A, Vaya A, Woodhams B, Mira Y et al. Contribution of polymorphisms in the endothelial protein C receptor gene to soluble endothelial protein C receptor and circulating activated protein C levels, and thrombotic risk. *Thromb Haemost* 2004; 91(5):905-911.

115. Medina P, Navarro S, Estelles A, Vaya A, Bertina RM, Espana F. Influence of the 4600A/G and 4678G/C polymorphisms in the endothelial protein C receptor (EPCR) gene on the risk of venous thromboembolism in carriers of factor V Leiden. *Thromb Haemost* 2005; 94(2):389-394.

116. Saposnik B, Reny JL, Gaussem P, Emmerich J, Aiach M, Gandrille S. A haplotype of the EPCR gene is associated with increased plasma levels of sEPCR and is a candidate risk factor for thrombosis. *Blood* 2004; 103(4):1311-1318.

117. Francis CW. Plasminogen activator inhibitor-1 levels and polymorphisms. *Arch Pathol Lab Med* 2002; 126(11):1401-1404.

118. Dawson S, Hamsten A, Wiman B, Henney A, Humphries S. Genetic variation at the plasminogen activator inhibitor-1 locus is associated with altered levels of plasma plasminogen activator inhibitor-1 activity. *Arterioscler Thromb* 1991; 11(1):183-190.

119. Segui R, Estelles A, Mira Y, Espana F, Villa P, Falco C et al. PAI-1 promoter 4G/5G genotype as an additional risk factor for venous thrombosis in subjects with genetic thrombophilic defects. *Br J Haematol* 2000; 111(1):122-128.

120. Zhao L, Morser J, Bajzar L, Nesheim M, Nagashima M. Identification and characterization of two thrombin-activatable fibrinolysis inhibitor isoforms. *Thromb Haemost* 1998; 80(6):949-955.

121. Henry M, Aubert H, Morange PE, Nanni I, Alessi MC, Tiret L et al. Identification of polymorphisms in the promoter and the 3' region of the TAFI gene: evidence that plasma TAFI antigen levels are strongly genetically controlled. *Blood* 2001; 97(7):2053-2058.

122. Martini CH, Brandts A, de Bruijne EL, van Hylckama Vlieg A, Leebeek FW, Lisman T et al. The effect of genetic variants in the thrombin activatable fibrinolysis inhibitor (TAFI) gene on TAFI-antigen levels, clot lysis time and the risk of venous thrombosis. *Br J Haematol* 2006; 134(1):92-94.

123. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost* 2005; 3(2): 292-299.

124. Bezemer ID, Doggen CJM, Vos HL, Rosendaal FR. No Association Between the Common MTHFR 677C->T Polymorphism and Venous Thrombosis: Results From the MEGA Study. *Arch Intern Med* 2007; 167(5):497-501.

125. Water N, Tan T, Ashton F, O'grady A, Day T, Browett P et al. Mutations within the protein Z-dependent protease inhibitor gene are associated with venous thromboembolic disease: a new form of thrombophilia. *Br J Haematol* 2004; 127(2):190-194.

126. Al Shanqeeti A, van Hylckama Vlieg A, Berntorp E, Rosendaal FR, Broze GJ, Jr. Protein Z and protein Z-dependent protease inhibitor. Determinants of levels and risk of venous thrombosis. *Thromb Haemost* 2005; 93(3):411-413.

127. Gonzalez-Conejero R, Perez-Ceballos E, Vicente V, Corral J. Protein Z-dependent protease inhibitor W303X mutation in venous thrombosis. *Br J Haematol* 2005; 129(4):561-562.

128. Corral J, Gonzalez-Conejero R, Soria JM, Gonzalez-Porras JR, Perez-Ceballos E, Lecumberri R et al. A nonsense polymorphism in the protein Z-dependent protease inhibitor increases the risk for venous thrombosis. *Blood* 2006; 108(1):177-183.

129. Tarumi T, Kravtsov DV, Moore JH, Williams SM, Gailani D. Common single nucleotide polymorphisms in the promoter region of the human factor XI gene. *J Thromb Haemost* 2003; 1(8):1854-1856.

130. de Visser MCH, Poort SR, Vos HL, Rosendaal FR, Bertina RM. Factor X levels, polymorphisms in the promoter region of factor X, and the risk of venous thrombosis. *Thromb Haemost* 2001; 85(6):1011-1017.

131. Le Flem L, Picard V, Emmerich J, Gandrille S, Fiessinger JN, Aiach M et al. Mutations in promoter region of thrombomodulin and venous thromboembolic disease. *Arterioscler Thromb Vasc Biol* 1999; 19(4):1098-1104.

132. Le Flem L, Mennen L, Aubry ML, Aiach M, Scarabin PY, Emmerich J et al. Thrombomodulin promoter mutations, venous thrombosis, and varicose veins. *Arterioscler Thromb Vasc Biol* 2001; 21(3):445-451.

133. Thude H, Wilkens A, Anders O, Barz D. Analysis of the thrombomodulin gene in patients with venous thrombosis. *Thromb Res* 2002; 107(3-4):109-114.

134. Heit JA, Petterson TM, Owen WG, Burke JP, DE Andrade M, Melton LJ, III. Thrombomodulin gene polymorphisms or haplotypes as potential risk factors for venous thromboembolism: a population-based case-control study. *J Thromb Haemost* 2005; 3(4):710-717.

135. Rosendaal FR. Risk factors for venous thrombotic disease. *Thromb Haemost* 1999; 82(2):610-619.

136. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* 1995; 10(1):111-113.

137. Jacques PF, Bostom AG, Williams RR, Ellison RC, Eckfeldt JH, Rosenberg IH et al. Relation between folate status, a common mutation in methylenetetrahydrofolate reductase, and plasma homocysteine concentrations. *Circulation* 1996; 93(1):7-9.

138. Den Heijer M, Koster T, Blom HJ, Bos GMJ, Briët E, Reitsma PH et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. *N Engl J Med* 1996; 334(12):759-762.

139. Ray JG, Shmorgun D, Chan WS. Common C677T polymorphism of the methylenetetrahydrofolate reductase gene and the risk of venous thromboembolism: meta-analysis of 31 studies. *Pathophysiol Haemost Thromb* 2002; 32(2):51-58.

140. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002; 325(7374):1202.

141. Callaham ML, Wears RL, Weber EJ, Barton C, Young G. Positive-outcome bias and other limitations in the outcome of research abstracts submitted to a scientific meeting. *JAMA* 1998; 280(3):254-257.

142. Cattaneo M, Tsai MY, Bucciarelli P, Taioli E, Zighetti ML, Bignell M et al. A common mutation in the methylenetetrahydrofolate reductase gene (C677T) increases the risk for deep-vein thrombosis in patients with mutant factor V (factor V:Q506). *Arterioscler Thromb Vasc Biol* 1997; 17(9):1662-1666.

143. Kluijtmans LAJ, Den Heijer M, Reitsma PH, Heil SG, Blom HJ, Rosendaal FR. Thermolabile methylenetetrahydrofolate reductase and factor V Leiden in the risk of deep-vein thrombosis. *Thromb Haemost* 1998; 79(2):254-258.

144. Margaglione M, D'Andrea G, d'Addedda M, Giuliani N, Cappucci G, Iannaccone L et al. The methylenetetrahydrofolate reductase TT677 genotype is associated with venous thrombosis independently of the coexistence of the FV Leiden and the prothrombin A20210 mutation. *Thromb Haemost* 1998; 79(5):907-911.

145. Alhenc-Gelas M, Arnaud E, Nicaud V, Aubry ML, Fiessinger JN, Aiach M et al. Venous thromboembolic disease and the prothrombin, methylene tetrahydrofolate reductase and factor V genes. *Thromb Haemost* 1999; 81(4):506-510.

146. Cattaneo M, Chantarangkul V, Taioli E, Santos JH, Tagliabue L. The G20210A mutation of the prothrombin gene in patients with previous first episodes of deep-vein thrombosis: prevalence and association with factor V G1691A, methylenetetrahydrofolate reductase C677T and plasma prothrombin levels. *Thromb Res* 1999; 93(1):1-8.

147. Gemmati D, Serino ML, Trivellato C, Fiorini S, Scapoli GL. C677T substitution in the methylenetetrahydrofolate reductase gene as a risk factor for venous thrombosis and arterial disease in selected patients. *Haematologica* 1999; 84(9):824-828.

148. Hessner MJ, Dinauer DM, Luhm RA, Endres JL, Montgomery RR, Friedman KD. Contribution of the glycoprotein Ia 807TT, methylene tetrahydrofolate reductase 677TT and prothrombin 20210GA genotypes to prothrombotic risk among factor V 1691GA (Leiden) carriers. *Br J Haematol* 1999; 106(1):237-239.

149. Rintelen C, Mannhalter C, Lechner K, Eichinger S, Kyrle PA, Papagiannopoulos M et al. No evidence for an increased risk of venous thrombosis in patients with factor V Leiden by the homozygous 677 C to T mutation in the methylenetetrahydrofolate-reductase gene. *Blood Coagul Fibrinolysis* 1999; 10(2):101-105.

150. Fujimura H, Kawasaki T, Sakata T, Ariyoshi H, Kato H, Monden M et al. Common C677T polymorphism in the methylenetetrahydrofolate reductase gene increases the risk for deep vein thrombosis in patients with predisposition of thrombophilia. *Thromb Res* 2000; 98(1):1-8.

151. Gaustadnes M, Rudiger N, Moller J, Rasmussen K, Bjerregaard LT, Ingerslev J. Thrombophilic predisposition in stroke and venous thromboembolism in Danish patients. *Blood Coagul Fibrinolysis* 1999; 10(5):251-259.

152. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004; 291(5):565-575.

153. Bonaa KH, Njolstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006; 354(15):1578-1588.

154. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006; 354(15):1567-1577.

155. Den Heijer M, Willems HP, Blom HJ, Gerrits WB, Cattaneo M, Eichinger S et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: A randomized, placebo-controlled, double-blind trial. *Blood* 2007; 109(1):139-144.

156. D'Angelo A, Coppola A, Madonna P, Fermo I, Pagano A, Mazzola G et al. The role of vitamin B12 in fasting hyperhomocysteinemia and its interaction with the homozygous C677T mutation of the methylenetetrahydrofolate reductase (MTHFR) gene. A case-control study of patients with early-onset thrombotic events. *Thromb Haemost* 2000; 83(4): 563-570.

157. Harrington DJ, Malefora A, Schmeleva V, Kapustin S, Papayan L, Blinov M et al. Genetic variations observed in arterial and venous thromboembolism--relevance for therapy, risk prevention and prognosis. *Clin Chem Lab Med* 2003; 41(4):496-500.

158. Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost* 2001; 86(1):452-463.

159. Stein PD, Patel KC, Kalra NK, El Baage TY, Savarapu P, Silbergleit A et al. Deep venous thrombosis in a general hospital. *Chest* 2002; 122(3):960-962.

160. Souto JC, Almasy L, Borrell M, Blanco-Vaca F, Mateo J, Soria JM et al. Genetic susceptibility to thrombosis and its relationship to physiological risk factors: the GAIT study. Genetic Analysis of Idiopathic Thrombophilia. *Am J Hum Genet* 2000; 67(6):1452-1459.

161. Larsen TB, Sorensen HT, Skytthe A, Johnsen SP, Vaupel JW, Christensen K. Major genetic susceptibility for venous thromboembolism in men: a study of Danish twins. *Epidemiology* 2003; 14(3):328-332.

162. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de RH et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994; 369(6475):64-67.

163. Hasstedt SJ, Bovill EG, Callas PW, Long GL. An unknown genetic defect increases venous thrombosis risk, through interaction with protein C deficiency. *Am J Hum Genet* 1998; 63(2):569-576.

164. Shiffman D, Ellis SG, Rowland CM, Malloy MJ, Luke MM, Iakoubova OA et al. Identification of four gene variants associated with myocardial infarction. *Am J Hum Genet* 2005; 77(4):596-605.

165. Germer S, Holland MJ, Higuchi R. High-throughput SNP allele-frequency determination in pooled DNA samples by kinetic PCR. *Genome Res* 2000; 10(2):258-266.

166. Shiffman D, O'Meara ES, Bare LA, Rowland CM, Louie JZ, Arellano AR et al. Association of gene variants with incident myocardial infarction in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol* 2008; 28(1):173-179.

167. Iakoubova OA, Tong CH, Chokkalingam AP, Rowland CM, Kirchgessner TG, Louie JZ et al. Asp92Asn polymorphism in the myeloid IgA Fc receptor is associated with myocardial infarction in two disparate populations: CARE and WOSCOPS. *Arterioscler Thromb Vasc Biol* 2006; 26(12):2763-2768.

168. Shiffman D, Rowland CM, Louie JZ, Luke MM, Bare LA, Bolonick JI et al. Gene variants of VAMP8 and HNRPUL1 are associated with early-onset myocardial infarction. *Arterioscler Thromb Vasc Biol* 2006; 26(7):1613-1618.

169. A haplotype map of the human genome. *Nature* 2005; 437(7063):1299-1320.

170. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005; 21(2):263-265.

171. Meijers JC, Tekelenburg WL, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000; 342(10):696-701.

172. Weir BS. *Genetic Data Analysis II Sunderland: Sinauer Associates Inc* 1996.

173. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A new and powerful approach to multiple testing. *Journal of the Royal Statistical Society* 1995;(Serials B(57)): 1289-1300.

174. Lee J, Jiao X, Hejtmancik JF, Kaiser-Kupfer M, Gahl WA, Markello TC et al. The metabolism of fatty acids in human Bietti crystalline dystrophy. *Invest Ophthalmol Vis Sci* 2001; 42(8):1707-1714.

175. Li A, Jiao X, Munier FL, Schorderet DF, Yao W, Iwata F et al. Bietti crystalline corneoretinal dystrophy is caused by mutations in the novel gene CYP4V2. *Am J Hum Genet* 2004; 74(5):817-826.

176. Gallimore MJ, Harris SL, Jones DW, Winter M. Plasma levels of factor XII, prekallikrein and high molecular weight kininogen in normal blood donors and patients having suffered venous thrombosis. *Thromb Res* 2004; 114(2):91-96.

177. Picard V, Nowak-Gottl U, Biron-Andreani C, Fouassier M, Frere C, Goualt-Heilman M et al. Molecular bases of antithrombin deficiency: twenty-two novel mutations in the antithrombin gene. *Hum Mutat* 2006; 27(6):600.

178. Massberg S, Gawaz M, Gruner S, Schulte V, Konrad I, Zohlnhofer D et al. A crucial role of glycoprotein VI for platelet recruitment to the injured arterial wall in vivo. *J Exp Med* 2003; 197(1):41-49.

179. Chung T, Connor D, Joseph J, Emmett L, Mansberg R, Peters M et al. Platelet activation in acute pulmonary embolism. *J Thromb Haemost* 2007; 5(5):918-924.

180. van Hylckama Vlieg A, van der Linden IK, Bertina RM, Rosendaal FR. High levels of factor IX increase the risk of venous thrombosis. *Blood* 2000; 95(12):3678-3682.

181. McGraw RA, Davis LM, Noyes CM, Lundblad RL, Roberts HR, Graham JB et al. Evidence for a prevalent dimorphism in the activation peptide of human coagulation factor IX. *Proc Natl Acad Sci U S A* 1985; 82(9):2847-2851.

182. Gerdes VE, Kraaijenhagen RA, Vogels EW, ten Cate H, Reitsma PH. Factor XI gene analysis in thrombophilia and factor XI deficiency. *J Thromb Haemost* 2004; 2(6):1015-1017.

183. Smith NL, Hindorff LA, Heckbert SR, Lemaitre RN, Marciante KD, Rice K et al. Association of genetic variations with nonfatal venous thrombosis in postmenopausal women. *JAMA* 2007; 297(5):489-498.

184. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007; 98(4):756-764.

185. Kyrle PA, Minar E, Hirschl M, Bialonczyk C, Stain M, Schneider B et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med* 2000; 343(7):457-462.

186. Bezemer ID, Bare LA, Doggen CJM, Arellano AR, Tong C, Rowland CM et al. Gene variants associated with deep vein thrombosis. *JAMA* 2008; 299(11):1306-1314.

187. Graham JB, Lubahn DB, Lord ST, Kirshtein J, Nilsson IM, Wallmark A et al. The Malmö polymorphism of coagulation factor IX, an immunologic polymorphism due to dimorphism of residue 148 that is in linkage disequilibrium with two other F.IX polymorphisms. *Am J Hum Genet* 1988; 42(4):573-580.

188. Khachidze M, Buil A, Viel KR, Porter S, Warren D, Machiah DK et al. Genetic determinants of normal variation in coagulation factor (F) IX levels: genome-wide scan and examination of the FIX structural gene. *J Thromb Haemost* 2006; 4(7):1537-1545.

189. Bauer KA, Kass BL, ten Cate H, Hawiger JJ, Rosenberg RD. Factor IX is activated in vivo by the tissue factor mechanism. *Blood* 1990; 76(4):731-736.

190. Iannone MA, Taylor JD, Chen J, Li MS, Rivers P, Slentz-Kesler KA et al. Multiplexed single nucleotide polymorphism genotyping by oligonucleotide ligation and flow cytometry. *Cytometry* 2000; 39(2):131-140.

191. Cooper H., Hedges LV. The Handbook of Research Synthesis. Newbury Park, CA: Russel Sage Foundation, 1994.

192. Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA. Score tests for association between traits and haplotypes when linkage phase is ambiguous. *Am J Hum Genet* 2002; 70(2):425-434.

193. Elashoff JD. NQuery Advisor Version 4.0 User's Guide. Los Angeles, CA: Statistical Solutions Limited, 2008.

194. Lowe GD. Factor IX and thrombosis. *Br J Haematol* 2001; 115(3):507-513.

195. Bezemer ID, Rosendaal FR. Predictive genetic variants for venous thrombosis: what's new? *Semin Hematol* 2007; 44(2):85-92.

196. Janssens AC, Aulchenko YS, Elefante S, Borsboom GJ, Steyerberg EW, van Duijn CM. Predictive testing for complex diseases using multiple genes: fact or fiction? *Genet Med* 2006; 8(7):395-400.

197. Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. *Genet Med* 2007; 9(8):528-535.

198. Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G et al. Cumulative association of five genetic variants with prostate cancer. *N Engl J Med* 2008; 358(9):910-919.

199. Sun J, Chang BL, Isaacs SD, Wiley KE, Wiklund F, Stattin P et al. Cumulative effect of five genetic variants on prostate cancer risk in multiple study populations. *Prostate* 2008; 68(12):1257-1262.

200. Lango H, Palmer CN, Morris AD, Zeggini E, Hattersley AT, McCarthy MI et al. Assessing the combined impact of 18 common genetic variants of modest effect sizes on type 2 diabetes risk. *Diabetes* 2008; 57(11):3129-3135.

201. van Hoek M, Dehghan A, Witteman JC, van Duijn CM, Uitterlinden AG, Oostra BA et al. Predicting type 2 diabetes based on polymorphisms from genome-wide association studies: a population-based study. *Diabetes* 2008; 57(11):3122-3128.

202. Gail MH. Discriminatory accuracy from single-nucleotide polymorphisms in models to predict breast cancer risk. *J Natl Cancer Inst* 2008; 100(14):1037-1041.

203. van Hylckama Vlieg A, Baglin CA, Bare LA, Rosendaal FR, Baglin TP. Proof of principle of potential clinical utility of multiple SNP analysis for prediction of recurrent venous thrombosis. *J Thromb Haemost* 2008; 6(5):751-754.

204. Cannegieter SC, Doggen CJM, van Houwelingen HC, Rosendaal FR. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). *PLoS Med* 2006; 3(8):e307.

205. Brown E, Bleetman A. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. Prophylaxis of venous thromboembolism in patients with lower limb plaster cast immobilisation. *Emerg Med J* 2007; 24(7):495-496.

206. Lapidus LJ, Ponzer S, Elvin A, Levander C, Larfars G, Rosfors S et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. *Acta Orthop* 2007; 78(4):528-535.

207. Patil S, Gandhi J, Curzon I, Hui AC. Incidence of deep-vein thrombosis in patients with fractures of the ankle treated in a plaster cast. *J Bone Joint Surg Br* 2007; 89(10): 1340-1343.

208. Moyer MP, Tracy RP, Tracy PB, van't Veer C, Sparks CE, Mann KG. Plasma lipoproteins support prothrombinase and other procoagulant enzymatic complexes. *Arterioscler Thromb Vasc Biol* 1998; 18(3):458-465.

209. Griffin JH, Kojima K, Banka CL, Curtiss LK, Fernandez JA. High-density lipoprotein enhancement of anticoagulant activities of plasma protein S and activated protein C. *J Clin Invest* 1999; 103(2):219-227.

210. Doggen C.J.M., Smith NL, Lemaitre RN, Heckbert SR, Rosendaal FR, Psaty BM. Serum lipid levels and the risk of venous thrombosis. *Arterioscler Thromb Vasc Biol* 2004; 24(10):1970-1975.

211. Deguchi H, Pecheniuk NM, Elias DJ, Averell PM, Griffin JH. High-density lipoprotein deficiency and dyslipoproteinemia associated with venous thrombosis in men. *Circulation* 2005; 112(6):893-899.

212. Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, Kliewer SA. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* 1998; 102(5):1016-1023.

213. Koelle MR, Horvitz HR. EGL-10 regulates G protein signaling in the C. elegans nervous system and shares a conserved domain with many mammalian proteins. *Cell* 1996; 84(1):115-125.

214. Ozaki K, Fujiwara T, Nakamura Y, Takahashi E. Isolation and mapping of a novel human kidney- and liver-specific gene homologous to the bacterial acetyltransferases. *J Hum Genet* 1998; 43(4):255-258.

215. Nossent AY, Smith NL, Eikenboom JCJ, Bertina RM, Rosendaal FR, Psaty BM. Associations of Blood Pressure and Antihypertensive Drugs with Plasma Levels of Coagulation Factor VIII. *Determinants of Plasma Levels of von Willebrand Factor and Coagulation Factor VIII (Thesis)* 2008;159-177.

216. Hahn Y, Lee B. Human-specific nonsense mutations identified by genome sequence comparisons. *Hum Genet* 2006; 119(1-2):169-178.

217. Joutsi-Korhonen L, Smethurst PA, Rankin A, Gray E, IJsseldijk M, Onley CM et al. The low-frequency allele of the platelet collagen signaling receptor glycoprotein VI is associated with reduced functional responses and expression. *Blood* 2003; 101(11):4372-4379.

218. Croft SA, Samani NJ, Teare MD, Hampton KK, Steeds RP, Channer KS et al. Novel platelet membrane glycoprotein VI dimorphism is a risk factor for myocardial infarction. *Circulation* 2001; 104(13):1459-1463.

219. Takagi S, Iwai N, Baba S, Mannami T, Ono K, Tanaka C et al. A GPVI polymorphism is a risk factor for myocardial infarction in Japanese. *Atherosclerosis* 2002; 165(2):397-398.

220. Cole VJ, Staton JM, Eikelboom JW, Hankey GJ, Yi Q, Shen Y et al. Collagen platelet receptor polymorphisms integrin alpha2beta1 C807T and GPVI Q317L and risk of ischemic stroke. *J Thromb Haemost* 2003; 1(5):963-970.

221. Ollikainen E, Mikkelsson J, Perola M, Penttila A, Karhunen PJ. Platelet membrane collagen receptor glycoprotein VI polymorphism is associated with coronary thrombosis and fatal myocardial infarction in middle-aged men. *Atherosclerosis* 2004; 176(1):95-99.

222. Bray PF, Howard TD, Vittinghoff E, Sane DC, Herrington DM. Effect of genetic variations in platelet glycoproteins Ibalpha and VI on the risk for coronary heart disease events in postmenopausal women taking hormone therapy. *Blood* 2007; 109(5):1862-1869.

223. Hovens MM, Snoep JD, Tamsma JT, Huisman MV. Aspirin in the prevention and treatment of venous thromboembolism. *J Thromb Haemost* 2006; 4(7):1470-1475.

224. Watson HG, Chee YL. Aspirin and other antiplatelet drugs in the prevention of venous thromboembolism. *Blood Rev* 2008; 22(2):107-116.

225. Kitchens CS. The contact system. *Arch Pathol Lab Med* 2002; 126(11):1382-1386.