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The angiotensin-converting enzyme gene insertion/deletion polymorphism: insufficient evidence for a role in deep venous thrombosis

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The angiotensin-converting enzyme (ACE) I/D polymorphism is an insertion/deletion of an ALU-repeat sequence of 287 base pairs (bp) in intron 16 of the ACE gene, located at 17q23. This results in three genotypes: II, ID and DD, with individuals with the DD genotype having about 40–50% higher circulating plasma ACE levels than individuals with the II genotype and individuals with the ID genotype having intermediate levels [1,2].

ACE plays a role in platelet activation and aggregation and a reduced fibrinolysis [3]. Increased ACE levels could therefore theoretically lead to an increased risk of thrombosis, a hypothesis which is supported by the finding that ACE-inhibitors have an antithrombotic effect in rat models [4].

Several studies have focused on the relationship between the DD genotype and the occurrence of thrombosis. In individuals following total hip arthroplasty, Philipp *et al.* found a considerably increased risk of thrombotic events for individuals carrying the DD genotype compared with individuals carrying the II genotype [odds ratio (OR) 11.7, 95% confidence interval (CI): 2.3–84.5] [5]. Subsequent studies yielded conflicting results, with some reporting an increased risk of thrombosis for individuals with the DD genotype [6–9], and others not finding any association between the I/D polymorphism and thrombosis [10–13].

We investigated the relationship between this polymorphism and deep venous thrombosis (DVT) in a large case-control study, the Leiden Thrombophilia Study (LETS), which has been described in detail elsewhere [14]. In short, 474 patients with an objectively confirmed first episode of DVT from three Dutch anticoagulation centers and 474 age- and sex-matched control subjects from the same geographic area were enrolled. Subjects with a known malignant disorder were excluded. The ACE I/D genotype is determined by

polymerase chain reaction, as also described by Rigat *et al.* [15]. Results were obtained for 471 cases and 472 control subjects (see Table 1).

Genotypes of controls were in Hardy–Weinberg equilibrium ($\chi^2 = 0.006$, $P = 0.94$); the frequency of the D-allele among controls was 0.51, which is consistent with frequencies reported in other Caucasian populations [16]. The risk estimates, i.e. OR and 95% CI of the different genotypes, are summarized in Table 1.

Contrary to expectations we found a slight protective effect of the D-allele with regard to deep venous thrombosis (OR DD vs. II: 0.7, 95% CI 0.5–1.0). When the subjects were stratified by sex, it became clear that the low overall risk for the D allele was due almost entirely to a reduced risk in women (DD vs. II women OR: 0.5, 95% CI: 0.3–0.9; men OR: 0.9, 95% CI 0.5–1.6). In men, no protective effect of the D-allele was found regardless of age, but the overall protective effect in women in our study was found to be restricted to women younger than 50 years of age (DD vs. II women < 50 years OR: 0.4, 95% CI: 0.2–0.7; women > 50 years OR: 1.1, 95% CI: 0.4–2.7). Adjustment for age and several other possible thrombophilic traits (use of an oral contraceptive, pre/postmenopausal status) did not affect these results.

Gonzalez Ordenez *et al.* found a protective effect of the D allele in Spanish men [11]. Recently, Wells *et al.* also reported a protective effect on the risk of venous thrombosis

Table 1 Odds ratio and 95% confidence interval for different insertion/deletion genotypes

Subgroup	Genotype	Cases <i>n</i> = 471	Controls <i>n</i> = 472	OR (95% CI)
All	II	125	112	1*
	ID	252	235	1.0 (0.7–1.3)
	DD	94	125	0.7 (0.5–1.0)
Men	II	55	52	1*
	ID	99	100	0.9 (0.6–1.5)
	DD	48	49	0.9 (0.5–1.6)
Women	II	70	60	1*
	ID	153	135	1.0 (0.6–1.5)
	DD	46	76	0.5 (0.3–0.9)

*Reference category.

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associated with the D allele, although not significant after restricting to patients with a first venous thrombotic event [17]. In the latter study, the protective effect seemed more pronounced in men than in women, although subgroups were small. Even though our result is statistically significant at the 5% level, the upper limit of the 95% CI approaches 1.0, and thus a type I error could be the cause, in particular as a protective effect is difficult to explain.

There are several possible explanations for the diverse results on the association between the I/D genotype and the risk of thrombosis. Firstly, the studies varied widely in the types of patients investigated, e.g. surgery patients [5,10], pregnant women [6]. Secondly, inclusion criteria differed as to whether only patients with a first event of thrombosis were included (current study) or patients with a history of thrombosis.

In addition, the studies with smaller numbers of participants tend to report higher odds ratios than the larger studies. This could suggest publication bias, but it could also be that in the specific subgroups investigated in the smaller studies (postoperative subjects, African-Americans, pregnant women) carrying the D allele does indeed result in a higher risk of developing thrombosis than it does in the larger samples of unselected patients.

Ethnic background may also play a role. The smaller studies reporting a high relative risk mainly originated from the United States (sometimes including only, or many African-Americans), while larger studies mainly originate from Europe or Canada. Differences could be due to chance fluctuation, but perhaps differences in gene–gene and environment–gene interactions play a role.

There is increasing evidence that the I/D polymorphism is not the functional polymorphism determining ACE levels, but that it is in LD with a functional variant located more to the 3' region of the ACE gene [18–21]. In conclusion, the results of this study provide insufficient evidence of an association between the ACE I/D polymorphism and the risk of deep venous thrombosis.

References

- 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**: 1343–6.
- Tiret L, Rigat B, Visvikis S, Breda C, Corvol P, Cambien F, Soubrier F. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. *Am J Hum Genet* 1992; **51**: 197–205.
- Brown NJ, Vaughan DE. Prothrombotic effects of angiotensin. *Adv Intern Med* 2000; **45**: 419–29.
- Chabielska E, Pawlak R, Buczek W. Effects of drugs affecting the rennin–angiotensin system on venous thrombosis in normotensive rats. *Pol J Pharmacol* 1996; **48**: 89–91.
- Philipp CS, Dilley A, Saidi P, Evatt B, Austin H, Zawadsky J, Harwood D, Ellingsen D, Barnhart E, Phillips DJ, Hooper WC. Deletion polymorphism in the angiotensin-converting enzyme gene as a thrombophilic risk factor after hip arthroplasty. *Thromb Haemost* 1998; **80**: 869–73.
- Dilley A, Austin HEL, Jamil M, Hooper WC, Barnhart E, Evatt BL, Sullivan PS, Ellingsen D, Patterson-Barnett A, Eller D, Randall H, Philipp C. Genetic factors associated with thrombosis in pregnancy in a United States population. *Am J Obstet Gynecol* 2000; **183**: 1271–7.
- Hooper WC, Dowling NF, Wenger NK, Dilley A, Ellingsen D, Evatt BL. Relationship of venous thromboembolism and myocardial infarction with the renin–angiotensin system in African-Americans. *Am J Hematol* 2002; **70**: 1–8.
- Von Depka M, Czwalinna A, Wermes C, Eisert R, Scharrer I, Ganser A, Ehrenforth S. The deletion polymorphism in the angiotensin-converting enzyme gene is a moderate risk factor for venous thromboembolism. *Thromb Haemost* 2003; **89**: 847–52.
- Fatini C, Gensini F, Sticchi E, Battaglini B, Prisco D, Fedi S, Brunelli T, Marcucci R, Conti AA, Gensini GF, Abbate R. ACE DD genotype: an independent predisposition factor to venous thromboembolism. *Eur J Clin Invest* 2003; **33**: 642–7.
- Della Valle C, Issack PS, Baitner A, Steiger DJ, Fang C, Di Cesare PE. The relationship of the factor V Leiden mutation or the deletion–deletion polymorphism of the angiotensin converting enzyme to postoperative thromboembolic events following total joint arthroplasty. *BMC Musculoskelet Disord* 2001; **2**: 1.
- Gonzalez Ordenez AJ, Fernandez Carreira JM, Medina Rodriguez JM, Martin SL, Alvarez DR, Alvarez Martinez MV, Coto GE. Risk of venous thromboembolism associated with the insertion/deletion polymorphism in the angiotensin-converting enzyme gene. *Blood Coagul Fibrinolysis* 2000; **11**: 485–90.
- Jackson A, Brown K, Langdown J, Luddington R, Baglin T. Effect of the angiotensin-converting enzyme gene deletion polymorphism on the risk of venous thromboembolism. *Br J Haematol* 2000; **111**: 562–4.
- Köppel H, Renner W, Gugl A, Cichocki L, Gasser R, Wascher TC, Pilger E. The angiotensin-converting-enzyme insertion/deletion polymorphism is not related to venous thrombosis. *Thromb Haemost* 2004; **91**: 76–9.
- Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. *Lancet* 1993; **342**: 1503–6.
- Rigat B, Hubert C, Corvol P, Soubrier F. PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). *Nucl Acids Res* 1992; **20**: 1433.
- Agerholm-Larsen B, Nordestgaard BG, Tybjaerg-Hansen A. ACE gene polymorphism in cardiovascular disease: meta-analyses of small and large studies in whites. *Arterioscler Thromb Vasc Biol* 2000; **20**: 484–92.
- Wells PS, Rodger MA, Forgie MA, Langlois NJ, Armstrong L, Carson NL, Jaffey J. The ACE D/D genotype is protective against the development of idiopathic deep vein thrombosis and pulmonary embolism. *Thromb Haemost* 2003; **90**: 829–34.
- Keavney B, McKenzie CA, Connell JM, Julier C, Ratcliffe PJ, Sobel E, Lathrop M, Farrall M. Measured haplotype analysis of the angiotensin-I converting enzyme gene. *Hum Mol Genet* 1998; **7**: 1745–51.
- McKenzie CA, Abecasis GR, Keavney B, Forrester T, Ratcliffe PJ, Julier C, Connell JM, Bennett F, McFarlane-Anderson N, Lathrop GM, Cardon LR. Trans-ethnic fine mapping of a quantitative trait locus for circulating angiotensin I-converting enzyme (ACE). *Hum Mol Genet* 2001; **10**: 1077–84.
- Zhu X, McKenzie CA, Forrester T, Nickerson DA, Broeckel U, Schunkert H, Doering A, Jacob HJ, Cooper RS, Rieder MJ. Localization of a small genomic region associated with elevated ACE. *Am J Hum Genet* 2000; **67**: 1144–53.
- Zhu X, Bouzekri N, Southam L, Cooper RS, Adeyemo A, McKenzie CA, Luke A, Chen G, Elston RC, Ward R. Linkage and association analysis of angiotensin I-converting enzyme (ACE)–gene polymorphisms with ACE concentration and blood pressure. *Am J Hum Genet* 2001; **68**: 1139–48.