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Absence of the Prothrombin Gene Variant in Koreans

Dear Sir,

A recently described genetic variant of the prothrombin gene (G to A transition at nucleotide position 20210) is associated with an increased risk of venous thrombosis (1). The 20210A prothrombin allele may precipitate cerebral ischemia or myocardial infarction in young patients with known prothrombotic abnormalities (2, 3). Similarly, it has been demonstrated that factor V Leiden further increases the risk of venous thrombosis in patients with inherited coagulation disorders (4). However, there are marked ethnic variations in the prevalence of factor V Leiden, which has been reported to be absent in Korean population (5, 6). The prevalence of prothrombin gene variant may also be different among individuals of different racial groups. We therefore investigated the frequency of prothrombin gene variant (20210A) in patients with thrombosis and randomly selected patients without a history of thromboembolic disease.

The patient study group (n = 154; 69 men and 85 women) included 109 unrelated individuals (median age 57 years, range 20-86 years) who had been referred due to the venous or arterial thrombotic events (21 deep vein thrombosis, 7 pulmonary embolism, 4 isolated mesenteric or portal veins, 62 stroke, 7 myocardial infarct, 8 peripheral artery obstructive diseases), and 45 patients without thrombotic episode.

To identify the prothrombin gene variant (20210A), 142-bp DNA fragment was obtained by amplification of genomic DNAs, and then digested using the *Hind*III endonuclease, as previously described (7). None of the subjects within this study group were found to have the mutation.

This finding suggests that, as for factor V Leiden (5, 6), the 20210A prothrombin mutation is very rare, among the Korean population. Further investigation is needed to determine whether the detection of 20210A prothrombin may be of value in subgroups of patients with thrombosis.

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References

1. 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 increase in venous thrombosis. Blood 1996; 88: 3698-703.
2. Bentolila S, Ripoll L, Drouet L, Mazoyer E. Thrombophilia due to 20210 G->A prothrombin polymorphism and cerebral ischemia in the young. Stroke 1997; 28: 1846-7.
3. Rosendaal FR, Siscovick DS, Schwartz SM, Psaty BM, Raghunathan TE, Vos HL. A common prothrombin variant (20210 G to A) increases the risk of myocardial infarction in young women. Blood 1997; 90: 1747-50.
4. Koelman BPC, Reitsma PH, Allaart CF, Bertina RM. Activated protein C resistance as an additional risk factor for thrombosis in protein C deficient families. Blood 1994; 84: 1031-4.
5. Song KS, Choi CR, Park Q, Lee A. Very low incidence of Arg506->Gln mutation in the factor V gene among Korean population. Thromb Haemost 1997; suppl: 223.
6. Kim YW, Yoon KY, Park S, Shim YS, Cho HI, Park SS. Absence of factor V Leiden mutation in Koreans. Thromb Res 1997; 86: 181-2.
7. Makris M, Preston FE, Beauchamp NJ, Cooper PC, Daly ME, Hampton KK, Bayliss P, Peake IR, Miller GJ. Co-inheritance of the 20210A allele of the prothrombin gene increases the risk of thrombosis in subjects with familial thrombophilia. Thromb Haemost 1997; 78: 1426-9.

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Prothrombin Gene Mutation (G 20210A) in Healthy Centenarians

Dear Sir,

A mutation in the 3' untranslated region of the prothrombin gene (G20210A) associated with higher plasma levels of prothrombin, is a common genetic risk factor for venous thrombosis (1). The prevalence of the G20210A prothrombin mutation in the heterozygous state varies from 0.7 to 4.0 %, and is higher in Southern than in Northern Europe, at variance with the factor V G1691A mutation (2, 3).

Genetic factors, in addition to environmental factors, are involved in determining the individual susceptibility to cardiovascular disease. Because a low frequency of genetic factors for cardiovascular disease could contribute to the longevity of a population, we evaluated the prevalence of the prothrombin G20210A mutation in a cohort of centenarians from Northern Italy and compared it with that found in a control group of healthy individuals encompassing a wide range of ages. Centenarians (n = 125; 31 males and 94 females; median age

102 years, range 100–109) were collected within a period of one year from the General Registry Offices, were ambulatory, self-sufficient, and lived in their homes in metropolitan communities of Northern Italy (Milan, Modena, Genova and the corresponding provinces) (4). Exclusion criteria were infection, inflammation, cancer, dementia, diabetes, renal and liver disease. Healthy individuals (n = 568; 207 males and 361 females, median age 45, range 14–79) were chosen from the general population from the same communities in Northern Italy. Arterial or venous thrombotic disease was excluded on the basis of clinical history and physical examination and using a structured validated questionnaire (4). Genomic DNA was prepared by standard techniques and the prothrombin mutation was detected by allele specific amplification (ASA) (5).

There were four heterozygotes (all women) among 125 centenarians (allele frequency 1.6%; 95% CI 0–1.6) and 16 (9 women and 7 men) among 568 controls (allele frequency 1.4%; 95% CI 0.7-2). Allele frequencies (1.6% vs 1.4%) did not differ in the two groups (p = 0.8; odds ratio 1.1 : 95% CI 0.4–3.5). None of the centenarians studied was homozygous for the G20210A mutation nor had a double defect (factor V G1691A and prothrombin G20210A mutations). Because there was a greater proportion of women among centenarians, 94 female centenarians were compared with 361 female controls. Allele frequencies were not substantially different from those found in the whole population. None of the controls had a double gene defect of factor V and prothrombin mutation. All the four centenarians heterozygous for the prothrombin G20210A mutation had been exposed during their long life to circumstantial thrombotic risk factors such as pregnancy, major surgery, trauma without any antithrombotic prophylaxis and yet they did not develop symptomatic deep venous thrombosis. As previously found for the factor V G1691A mutation (4, 6, 7), the prevalence of the 20210A allele is similar in centenarians and in healthy individuals, indicating that these mutations associated with thrombophilia are compatible with longevity and successful aging.

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References

1. 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: 3698-703 .
2. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet 1995; 346: 1133-4.
3. Rosendaal FR, Doggen CJM, Zivelin A, Arruda VR, Aiach M, Siscovick DS, Hillarp A, Watzke HH, Bernardi F, Cumming AM, Preston FE, Reitsma PH. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost 1998; 79: 706-8.
4. Mari D, Mannucci PM, Duca F, Bertolini S, Franceschi C. Mutant factor V (Arg506Gln) in healthy centenarians. Lancet 1996; 347: 1044 (letter).
5. Hézard N, Cornillet-Lefebvre P, Gillot L, Potron G, Nguyen P. Multiplex ASA PCR for a simultaneous determination of factor V Leiden gene, G-A 20210 prothrombin gene and C-T 677 MTHFR gene mutations. Thromb Haemost 1998; 79: 1054 (letter).
6. Faure-Delanef L, Quéré I, Zouali H, Cohen D. Human longevity and R506Q factor V gene mutation. Thromb Haemost 1997; 78: 1160.
7. Kristensen SR, Andersen-Ranberg K, Bathum L, Jeune B. Factor V Leiden and venous thrombosis in Danish centenarians. Thromb Haemost 1998, 80: 860-1.

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Cerebral Vein Thrombosis not Related to Use of Oral Contraceptives in a 7-year-old Child Carrier of the Prothrombin 20210A Allele

Dear Sir,

Cerebral vein thrombosis is a rare and severe event which is frequently related with the use of oral contraceptives and/or the presence of inherited thrombophilia (1, 2). The most frequent inherited coagulation abnormalities reported in patients with cerebral vein thrombosis are the mutant alleles 1691A of the factor V gene (factor V Leiden) and 20210A of the prothrombin gene, accounting respectively for 20% and 15% of the cases in a large series of 40 patients (2). Intake of oral contraceptives is associated with a 13 to 22-fold increase in risk for cerebral vein thrombosis (1, 2); the increase in risk in women both carrying the prothrombin 20210A mutation and users of oral contraceptives was estimated to rise to 150-fold in comparison with non-carriers and non-users (2).

We evaluated a series of 20 patients (M/F 8/12) with cerebral vein thrombosis consecutively referred to our Center for laboratory evaluation since September 1994 through October 1998; the mean age at the moment of thrombosis was 30.6 years (median 31, range 3 to 52 years). Screening for inherited thrombophilia was carried out as previously described (3) and revealed inherited thrombophilia in 25% of cases (pro-

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