Factor V Leiden, prothrombin G20210A, and risk of sudden coronary death in apparently healthy individuals

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Factor V Leiden, Prothrombin G20210A, and Risk of Sudden Coronary Death in Apparently Healthy Persons

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Factor V Leiden and prothrombin G20210A are common mutations (in persons of European descent, the prevalence of Factor V Leiden ranges from 3% to 7% and the prevalence of prothrombin G20210A from 1% to 4%) and are well-established risk factors for venous thrombotic disease.[1] The relation between these 2 prothrombotic mutations and coronary heart disease remains controversial, but most previous studies included only patients with nonfatal ischemic events.[1,2] We hypothesized that a sudden, more severe ischemic outcome such as cardiac arrest may be differently related to an inherited predisposition to acute, occlusive coronary thrombosis. We therefore assessed the prevalence of 2 well-characterized prothrombotic mutations, factor V Leiden and prothrombin G20210A, in a population-based study of out-of-hospital sudden cardiac death.

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The basic design of this population-based case-control study has been described in detail previously.[3,4] For the current analysis, we included all cases of out-of-hospital cardiac arrest between July 1989 and June 1997 from whom a blood sample was collected in the field by paramedics in Seattle and suburban King County, Washington. Cases were defined as a sudden, pulseless condition in the absence of a noncardiac cause (e.g., trauma, drug overdose, respiratory failure, renal failure, end-stage liver disease, or cancer). Death certificates, medical examiner reports, and autopsy reports were examined when available to exclude noncardiac causes. Because the focus of the study was on persons who appeared healthy until their cardiac arrest, patients with a history of clinically recognized heart disease (angina pectoris, myocardial infarction, coronary artery bypass graft surgery, angioplasty, congestive heart failure, arrhythmias, cardiomyopathy, congenital or valvular disease) were also excluded. We further restricted the sudden cardiac death cases to married residents of King County, Washington, between the ages of 25 and 74 years. The reason for restricting the study to married persons relates to the high case fatality rate, which necessitated the collection of personal history and lifestyle data from spouses. Control subjects, matched to the case patients on sex and age (within 7 years), were randomly selected from the greater Seattle area using the sampling technique of random digit dialing. Control subjects also were married and free of clinically recognized heart disease and major comorbidities.

Blood samples were obtained within 45 minutes of cardiac arrest from 168 sudden cardiac death patients who had an intravenous line placed by paramedics, and from 606 control subjects at the time of the interview. Data regarding traditional cardiovascular risk factors (age, sex, race, height, weight, smoking history, physician-diagnosed hypertension, diabetes, hypercholesterolemia, and family history of myocardial infarction or sudden death) were obtained from the spouses of patients and from control subjects by

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TABLE 1 Characteristics of Sudden Coronary Death Cases and Control Subjects

Characteristic	Sudden Death Cases (n = 145)	Control Subjects (n = 592)
Mean age (yrs)	60 0	58 0
Men	80%	77%
White	93%	94%
Family history of cardiac arrest or MI	58%	40%
Family history of cardiac arrest only	33%	25%
Family history of MI only	53%	34%
Current smokers	35%	10%
Body mass index >30 kg/m^2	17%	12%
Physician diagnosis of		
Hypertension	40%	23%
Diabetes mellitus	11%	4%
Hypercholesterolemia	30%	22%

MI = myocardial infarction

TABLE 2 Factor V Leiden, Prothrombin G20210A Mutations, and Risk of Sudden Coronary Death

	Cases (n = 145)		Controls (n = 592)		
Mutation	Negative	Positive	Negative	Positive	OR (95% CI)
Factor V	137 (96%)	6 (4%)	550 (94%)	37 (6%)	0 7 (0 3–1 6)
Prothrombin	141 (98%)	3 (2%)	573 (97%)	15 (3%)	0 8 (0 2–2 9)
Factor V or prothrombin	134 (94%)	9 (6%)	536 (9%)	51 (9%)	0 7 (0 3–1 5)

in-person interview according to a protocol approved by the University of Washington Human Subjects Committee The reliability of spousal reports in this study has been demonstrated previously [3 4]

Genomic deoxyribonucleic acid extraction from peripheral blood samples and genotyping for the factor V Leiden and prothrombin G20210A mutations were performed as previously described [5 6] Of the 168 sudden cardiac death cases and 606 control subjects from whom blood specimens were collected, analyzable deoxyribonucleic acid was available for 145 cases (86%) and 592 controls (98%) Logistic regression models were used to assess the relation between genotype and risk of sudden cardiac death, as estimated by the odds ratio (OR) and 95% confidence interval (CI), as well as to adjust for potential confounders such as age and other traditional coronary risk factors

Characteristics of the 145 sudden coronary death cases and 592 control subjects are lissted in Table 1 The mean age of the study subjects was 59 years, approximately 80% were men and >90% were white Traditional cardiovascular risk factors (smoking, obesity, hypertension, diabetes, hypercholesterolemia, and positive family history) were more common among the sudden cardiac death cases than among controls (Table 1) The distribution of traditional cardiovascular risk factors was similar among subjects with and without blood specimens available for genotyping for cases and controls (data not shown)

Neither the factor V Leiden nor prothrombin G20210A mutations were associated with increased risk of sudden cardiac death (Table 2) Overall, the risk estimates were in the range of 0 7 to 0 8, but the 95% CIs overlapped 1 0 Restriction of the analyses to subjects of European descent, or adjustment for age or other traditional cardiovascular risk factors, did not appreciably alter these results (data not shown)

We performed additional analyses of the risk of sudden cardiac death associated with the prothromobotic mutations stratified by age and sex The risk estimate associated with carrying factor V Leiden appeared to be lower among the 258 subjects aged ≤55 years (OR 0 3, 95% CI 0 04 to 2 7) than among the 474 subjects aged >55 (OR 0 8, 95% CI 0 3 to 2 2) In contrast, the OR associated with prothrombin G20210A was 1 2 (95% CI 0 1 to 10 2) among the younger subgroup compared with 0 7 (95% CI 0 1 to 3 2) among the older subgroup When analyzed by sex, the risk of sudden cardiac death associated with factor V Leiden appeared to be lower among the 569 men (OR 0 5, 95% CI 0 2 to 1 5) than among 161 women (OR 1 4, 95% CI 0 3 to 7 0) Similarly, the OR for sudden coronary death associated with prothrombin G20210A was 0 6 among men (95% CI 0 1 to 2 9) and 1 6 (95% CI 0 2 to 16 0) among women

When we stratified the risk of sudden cardiac death according to the presence or absence of other major cardiovascular risk factors, the OR associated with the presence of either factor V Leiden or prothrombin G20210A appeared to be lower among the 109 current smokers (OR 0 3, 95% CI 0 1 to 1 6) than among the 616 subjects who were not current smokers (OR 0 9, 95% CI 0 4 to 2 1) The risk associated with the presence of either mutation also appeared to be lower among the 172 subjects with (OR 0 2, 95% CI 0 02 to 1 7) than among the 556 subjects without (OR 1 0, 95% CI 0 4 to 2 1) hypercholesterolemia However, these subgroup comparisons most likely represent chance variation due to the relatively small subgroup sizes, and are not statistically significant There was also no evidence that the risk of sudden coronary death associated with either prothrombotic mutation was modified by hypertension, obesity, or diabetes (data not shown)

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Our population-based study did not find any evidence of an association of 2 well-characterized prothrombotic mutations, factor V Leiden and prothrombin G20210A, with increased risk of sudden coronary death A potentially important feature of the present study is the exclusion of cases and controls with a history of clinically recognized coronary heart disease, minimizing the potential influence of antithrombotic therapies and lifestyle modifications

Although our study is the first to examine the association of thrombosis-related gene variants and sudden coronary death among apparently healthy persons, several limitations are inherent in the present study. The exclusion of patients with prevalent heart disease was based on clinical criteria. However, most patients likely had underlying subclinical coronary atherosclerosis, which is generally present in >80% of patients who die suddenly of cardiac causes.[7] Although the lack of autopsy data in the present study precludes a precise estimate of coronary disease, the increased prevalence of traditional risk factors (e.g., smoking, hypertension, diabetes) among the cases compared with the controls is consistent with the presence of underlying coronary atherosclerosis in a significant proportion of the sudden death cases. Because of the community-based nature of the study, paramedics were able to obtain blood specimens only from patients for whom an intravenous line was placed as part of provision of emergency medical care once the patient was clinically stable or resuscitation had proved ineffective. Thus, the circumstances of the cardiac arrest or the provision of medical care often precluded the blood draw, and specimens for genotyping were available from only a fraction (~25%) of all sudden deaths that occurred during the study period, which may introduce some bias. However, the characteristics of study participants with and without blood drawn were similar among cases as well as controls. Although medical history data were collected through spousal interviews and not fully validated by medical record review, a small validation study demonstrated that spouses accurately provide information about demographics and common risk factors, such as smoking, hypertension, and diabetes.[4]

The present study indicates that 2 common prothrombotic mutations are not associated with increased susceptibility to sudden cardiac death among apparently healthy adults. Additional population and genetic studies that address other potential mechanisms, including arrhythmia initiation and propagation, are needed to elucidate the inherited risk determinants of sudden cardiac death risk in the general population.

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Relation of Degree of Laser Debulking of In-Stent Restenosis as a Predictor of Restenosis Rate

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Although balloon angioplasty of in-stent restenosis still has a recurrence rate as high as ≥80%,[1,2] brachytherapy presumably represented the most frequently used technique for treating in-stent restenosis in 2001; however, stenosis recurrence remained at a level of 17% to 28%.[3,4] Considering the degree of residual neointimal tissue, debulking the tissue is still the most logical treatment modality. The tissue of in-stent restenosis appears to be suitable for ablation with lasers, because it is highly cellular, soft, and free of calcifications.[5] Published data have disclosed high procedural success rates (>98%) and very low complication rates (<2%)[6,7] but revealed very heterogenous results owing to different lasing techniques, ongoing advances in laser technology, and inhomogeneous patient populations.[6–9] Because balloon angioplasty is already known to result in beneficial acute results and less experienced operators may finish laser ablation more quickly, the debulking effect has not clearly been differentiated from the balloon effect in these studies by examining the long-term results of those patients who had a sufficient debulking (diameter stenosis before adjunctive balloon angioplasty ≤30%).

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