

F5 Q506 Mutation and the Low Prevalence of Cardiovascular Disease in Canadian Inuit

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ABSTRACT

Background: The Keewatin Inuit have a very low age-adjusted mortality rate from vascular diseases compared to the general population of Canada. Interethnic differences in both genetic and lifestyle factors have been offered as explanations for this observation. We previously found that compared to white subjects, the Inuit had a significantly increased prevalence of 4 candidate alleles for atherosclerosis-related phenotypes, namely *AGT* T235, *FABP2* T54, *PONI* R192, and *APOE* E4, and a significantly decreased prevalence of 2 candidate alleles for atherosclerosis-related phenotypes, namely *ACE* D and *MTHFR* 677T.

Methods: We tested the hypothesis that 165 Canadian Inuit would have a significantly different frequency of the thrombosis-associated *F5* Q506 allele compared with

reference controls.

Results: We found a complete absence of *F5* Q506 in 165 Inuit, which was significantly different from the frequency of 3.92% observed in regional control White subjects.

Conclusions: The aggregate of results from our studies in Inuit to date suggests that the beneficial influence of the low prevalence of any or all of the *ACE* D, *MTHFR* 677T and *F5* Q506 outweighs the deleterious influence of the high prevalence of any or all of the other disease-associated alleles. However, it remains possible that other genetic and/or environmental factors determine the low susceptibility to vascular disease in the Inuit. (*J Investig Med* 1998;46:232-235)
Key words: coagulation • thrombosis • polygenic disease • genetic predisposition

INTRODUCTION

People indigenous to the arctic have a lower mortality from vascular disease than nonaboriginals.¹⁻³ This is surprising in light of their significantly increased prevalence of cigarette smoking.³ Even more striking is that there is a high prevalence of alleles for some candidate genes for vascular disease-related phenotypes in the Keewatin Inuit of Canada, namely *AGT* T235, *FABP2* T54, *PON* R192,

and *APOE* E4.⁴ This would suggest a genetic predisposition to vascular disease in the Keewatin Inuit. However, there is also a significantly decreased prevalence of other alleles for some candidate genes for vascular disease-related phenotypes in these people, namely *ACE* D and *MTHFR* 677T.^{4,5} This would suggest that there may be some degree of genetic resistance to vascular disease in the Keewatin Inuit. This apparent disparity in the conclusions regarding genetic resistance and susceptibility in the Inuit highlights the importance of continuing to study them to get a more complete picture of those factors that are related to the very low prevalence of vascular disease.

One possible newer genetic factor is factor V Leiden, which results from a G→A mutation at position 1691 in the *F5* gene, which substitutes glutamine (Q) for arginine at codon 506.⁶⁻⁸ *F5* Q506 encodes a form of factor Va that is resistant to degradation by activated protein C.⁶⁻⁸ Activated protein C resistance is a frequent cause of venous thromboembolism, with a prevalence of up to 50% in patients having a family history of venous throm-

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bosis.⁷ The procoagulant effect of the *F5* Q506 mutation may also predispose to arterial thrombosis.⁹⁻¹¹ We investigated the prevalence of the *F5* Q506 mutation in the Canadian Inuit to determine whether it was associated with the low prevalence of cardiovascular disease in the Keewatin Inuit.

METHODS

Subjects

The Northwest Territories of Canada are north of the 60th parallel and comprise one third of the land mass of the country. Of the 52,000 residents of the Northwest Territories in 1986, 35% were Inuit (Eskimo), 15% were Dene (Athapaskan Indians) and 50% were predominantly migrants of European origin from other parts of Canada. The traditional Inuit territory extends from the Chukchi Peninsula in northeastern Asiatic Russia, across Alaska and Northern Canada to Greenland. The present study involved residents of 8 communities from the Keewatin region of the Northwest Territories, mainly from the eastern coast adjacent to Hudson Bay.

A total of 516 randomly selected, unrelated individuals aged 18-80 years from the Keewatin region of the Northwest Territories were studied. Sufficient DNA was obtained from 306 individuals. Of these, 165 reported themselves as being Inuit, 51 were of European descent (white), 69 were of mixed ethnic descent, and 21 were of other ethnic backgrounds (non-white, non-Inuit).

Biochemical and Genetic Analysis

Plasma samples were obtained with informed consent. DNA was extracted according to established procedures. Genotyping for *F5* Q506 was accomplished using PCR amplification of DNA samples followed by digestion of the amplified products with endonuclease *Mnl* 1, as previously described.⁸ Known standard genotypic controls were run with each genotyping reaction.

Chi-square analysis was used to determine whether genotype frequencies deviated from those predicted by the Hardy-Weinberg law and to compare differences in allele frequencies between samples. Assuming an allele frequency for *F5* Q506 of 5% in white populations, we had a 70% or greater power to detect a reduction in this frequency of 0.8 (ie, an absolute frequency of 1% or less) in this number of study subjects, with a two-tailed alpha = 0.05.

RESULTS

The genotype frequencies for *F5* Q506 are shown in Table 1. The observed allele frequency of *F5* Q506 in the subsample of white subjects from the Keewatin region

Table 1: *F5* Q506 genotype number and frequency in ethnic groups in the Keewatin region.

	Inuit	Mixed	White	Other
Total number	165	69	51	21
Q506/R506 number	0	0	2	2
Q506/R506 frequency	0.0%	0.0%	3.96%	9.52%

was comparable to that observed in many other studies of this allele in normal control samples of white subjects.⁶ No homozygotes were identified in any of the ethnic groups studied. The genotype frequencies did not deviate from those predicted by the Hardy-Weinberg law in any of the subsamples (data not shown). An allele frequency of 0.0% was noted in both the Inuit and mixed ethnic groups. Allele frequencies of 3.92% and 9.52% were noted for the white and the other non-white, non-Inuit groups, respectively. There was a significant difference in the *F5* Q506 frequency between Inuit and white subsamples ($P < .01$).

DISCUSSION

We have shown a complete absence of the *F5* Q506 mutation from 165 Keewatin Inuit. Absence of this mutation has also been noted previously in smaller samples of Greenland Inuit¹² as well as of other aboriginal groups.¹³⁻¹⁵ Moreover, the prevalence of the *F5* Q506 mutation in several other non-white populations has been found to be either very low or nil,^{13,14} which supports the notion that the mutation is not present in aboriginal populations, but instead originated in European Whites. Ridker noted a carrier frequency of 1.25% among native Indians in the United States.¹⁶ This frequency might reflect the racial admixture that has occurred in some Native American communities in contrast with the absence of the mutation in more genetically isolated aboriginal communities.

Despite the small number of whites surveyed, the *F5* Q506 allele frequency of 3.92% in the subsample of white subjects in this study is comparable to that found in a random sample of Canadian blood donors¹⁷ and to that found in European samples.¹⁴ Considerable variation in the *F5* Q506 mutation prevalence exists among different European communities depending upon country of origin, with the highest frequencies occurring in Northern European communities.¹⁴ The absence of identified homozygotes on our study sample is not surprising in light of the relatively small number of white subjects tested.

The theoretical basis for a role of resistance to activat-

ed protein C and *F5* Q506 in acute coronary syndromes stems from the notion that thrombus formation following disruption of an atherosclerotic plaque is responsible for acute occlusion of coronary arteries leading to myocardial infarction (MI).¹⁸ Levels of several other components of the coagulation cascade, including factor VII, fibrinogen and plasminogen-activator inhibitor,¹⁹ have been associated with an increased risk of coronary artery disease.

Factor V is consumed in thrombus formation during acute MI; activated platelets release factor V from their alpha granules.²⁰ Failure to cleave and inhibit factor Va may lead to uncontrolled coagulation and intravascular thrombus formation and might also promote atherosclerosis within coronary arteries, since old thrombus can be an integral part of advanced atherosclerotic lesions.²¹ Furthermore, thrombin generation via factor Xa is strongly accelerated by endothelial cell bound factor Va,²² thereby promoting the growth of smooth muscle cells, which is an important step in atherogenesis.¹⁸ Thrombin also functions as a coagulation factor and as an agonist of platelet aggregation, chemotaxis, and proliferation important in atherogenesis.²³ Thus, *F5* Q506-related hypercoagulability may relate not only to intravascular thrombosis, but also to the severity of atherosclerosis.

The deleterious impact of *F5* Q506 can be exacerbated by other factors, such as plasma homocysteine and smoking.⁶ For example, when compared with women who did not smoke and did not carry *F5* Q506, women who both smoked and carried the mutation had a 30-fold increase in their risk of MI.¹¹ Moreover, the presence of additional risk factors, such as obesity, hypercholesterolemia, hypertension and diabetes, also increased the vascular disease risk associated with the presence of *F5* Q506.¹¹ Thus, the lack of consistency among clinical studies may reflect differences in the prevalence of other risk factors that act synergistically with *F5* Q506 to affect the risk of vascular disease.¹¹

In summary, we found a complete absence of the thrombosis-associated *F5* Q506 allele in 165 Inuit, which would be consistent with the known low prevalence of vascular disease in the Inuit people. The aggregate of our data from the Inuit to this point suggests that either: 1) the beneficial influence of the low prevalence of any or all of the *ACE* D, *MTHFR* 677T and *F5* Q506 outweighs the deleterious influence of the high prevalence of any or all of the other disease-associated alleles; or 2) these factors have no relationship with disease susceptibility and that other genetic and/or environmental factors determine the low susceptibility to vascular disease in the Inuit. The continued effort to identify and elucidate those factors that affect vascular disease susceptibility in the Inuit will be important for devising strategies to deal with the antic-

ipated increase in vascular disease in this race of people as their lifestyle changes.

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