ment, the anticoagulation therapy which was used for his deep venous thrombus might also have contributed to the resolution of intracardiac thrombus.

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Is there a heterozygote advantage for familial Mediterranean fever carriers against tuberculosis infections: Speculations remain?

Sirs,

Familial Mediterranean fever (FMF) is a disease characterized by recurrent episodes of fever and serosal inflammation accompanied by a marked acute phase response (1, 2). Mutations in the MEFV gene underlie familial Mediterranean fever and code for a protein called pyrin. The carrier frequency among North African Jews has been reported to be 1/5-1/10 (3) and 1/5 (21%) among Askhenazi Jews (1). Among Armenians it is expected to be as high as 1/3 (4). In a recent study we have shown the carrier rate in Turks to be 1/5 as well (5). The minimum prevalence of the disease is estimated to be 1/1073 in the Turkish population (2). These high numbers suggest that there is a possible heterozygote advantage to the inhabitants in the area.

A shared haplotype and mutation that is observed in Armenians. Askhenazi Jews and Druze FMF patients suggests that this mutation dates back at least 2000 years in the eastern Mediterranean basin. The historic retracing of another mutation suggests that it again dates back to at least 2500 years ago, again when these populations were living together in Mesopotamia. The first farmers in the history of mankind are known to have settled some 8000 years ago in the Fertile Crescent, an area extending from Mesopotamia into Anatolia (the mainland of Turkey). These farmers started to live together and raise cattle. Carriers of pyrin mutations in these geographically related populations might have shared a selective advantage, having adapted a new life style. The Anatolian people may have also received mutations during the migrations before the birth of Christ or may have fostered the mutation in their own land.

It has already been shown that carriers of certain hemolytic anemias are resistant to malaria, which was an organism that caused serious historical outbreaks in this area. In a parallel manner we wondered whether there

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could have been a candidate organism to offer a heterozygote advantage in the area. FMF patients and relatives have elevated CRP levels, suggesting an increased acute phase inflammatory response in these people (6). Thus the heterozygotes might simply have an advantage of mounting an augmented acute phase response to microorganisms. However, one wonders why this mutation was restricted to this area. Thus, a heightened resistance introduced by mutations in the MEFV gene to a pathogen endemic to the Eastern Mediterranean seems an attractive hypothesis to pursue.

Tuberculosis is an ancient disease caused by the tubercle bacillus. It has remained endemic in many areas for centuries. In humans the most common tubercle bacilli are Mycobacterium tuberculosis, which is transmitted by close contact, and Mycobac terium bovis that is transmitted by the consumption of milk from infected domestic animals. Thus, it would have been a new disease for the first farmers. These bacilli are intracellular pathogens. MEFV (the gene for familial Mediterranean fever) is primarily expressed in leukocytes and monocytes, and therefore might be expected to have an effect on immune function. We wanted to study whether heterozygotes for MEFV mutations had a better response to pathogens offering them a selective advantage. This pathogen would have to be some organism endemic to the Middle East. Since such a clue is not present we decided to investigate a possible advantage that could be introduced by an ancient pathogen - tuberculosis. An increased inflammatory response is required in the generation of cell-mediated immunity aimed at intracellular pathogens and to generate a delayed-type hypersensitivity response, that is characteristic of tuberculosis. In turn, patients with MEFV mutations have an augmented inflammatory response. Thus we decided to analyze whether carriers for the MEFV mutations had increased resistance to develop tuberculosis. We screened 103 patients with proven tuberculosis for the presence of MEFV mutations and compared the results with that published in 100 healthy Turkish individuals.

me DNA samples were isolated from the peri-

Table I. Frequencies for the common mutations in the MEFV gene among tuberculosis patients, healthy controls and FMF patients (%).

M694V	M680I	V726A	M694I	E148Q
3	5	2	-	12
3	1	4	-	9
51.5	9.2	2.8	0.4	3.5
	M694V 3 3 51.5	M694V M680I 3 5 3 1 51.5 9.2	M694V M680I V726A 3 5 2 3 1 4 51.5 9.2 2.8	M694V M680I V726A M694I 3 5 2 - 3 1 4 - 51.5 9.2 2.8 0.4

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pheral blood of patients with proven tuberculosis. The carrier frequency for the healthy Turkish population was previously determined from control samples consisting of the parents of children with various disorders (5). Informed consent was obtained from both groups. The DNA samples were tested for the five most frequent MEFV gene mutations, four in exon 10 (M694V, M680I, M694I, and V726A) and one in exon 2 (E148Q).

Tuberculosis in these patients was diagnosed by bacteriological confirmation in specimens.

The primer set used to amplify exon 10 is $Ex10F 5'[GC]_{40}GAG AAG CAG GAA GAG AGA TGC 3' and Ex10R 5'TAT CAT TGT TCT GGG CTC 3'. PCR products were subjected to electrophoresis on poly$ acrylamide. M680I and V726A mutations were confirmed by restriction analysis by Hinf I and Alu I after DGGE analysis. The mutation in exon 2 (E148Q) was analysed by Bst NI restriction enzyme digestion, after amplification of genomic DNA with previously defined primers. The comparison of the distribution of the MEFV gene mutations between tuberculosis patients and FMF carriers was done by the 2 test.

The carrier frequency in the Turkish population has previously been established as 1/5 and the mutation E148Q is the leading mutation (5) (Table I).

The age range of the tuberculosis patients was 16-63. There were 26 females and 77 males. Fifteen patients had a mutation in one allele and one patient was homozygous for the E148Q mutation. He did not have any symptoms related to FMF. Thus the car-

rier frequency among tuberculosis patients was almost 1/6. The difference with healthy controls was not significant (p > 0.05).

In the human genome mutations may be selected over centuries if they offer certain advantages for the selected population. The high carrier rate for the mutations in MEFV has suggested that these heterozygotes might also have a heightened resistance to an environmental factor. For the aforementioned reasons we believed the tubercle bacilli could have been a candidate pathogen to cause increased fitness in the carriers of MEFV mutations. However we have shown that the number of heterozygotes were not different among the tuberculosis patients as compared to healthy Turkish controls.

During attacks these patients have elevated levels of acute phase proteins such as ESR, CRP, SAA and fibrinogen. The acute phase proteins are induced by different cytokines. The simple reason for the selection of carriers may indeed be an elevated acute phase response that would enable an efficient response to pathogens. Further studies are required to explain the very high carrier rate in Middle Eastern populations.

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