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Worldwide Distribution of a Common Methylenetetrahydrofolate Reductase Mutation

To the Editor:

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is needed for methionine synthase to convert homocysteine to methionine. A reduction in MTHFR activity, such as that caused by the C→T missense mutation at position 677 of the MTHFR cDNA (C677T), which produces a thermolabile form of the enzyme, results in increased plasma homocysteine (Frosst et al. 1995). Homozygotes for the C677T mutation may have an increased risk of cardiovascular disease (Frosst et al. 1995) and neural tube defects (Wilcken 1997).

Folate is an important cofactor in the conversion of homocysteine to methionine; therefore, C677T homozygotes may require more folate for thermolabile MTHFR to function adequately. Insufficient folate intake during pregnancy can cause neural tube defects (Smithells et al. 1980); however, the role of folate in vascular disease is not well established.

Previous studies of the C677T mutation have concentrated on European populations. The allele frequency in Europeans is 24%–40% (van der Put et al. 1997), 26%–37% in Japanese populations (Papapetrou et al. 1997; Sohda et al. 1997), and ~11% in an African American population (Stevenson et al. 1997). We have screened 881 unrelated individuals from 16 worldwide populations for the presence of the C677T polymorphism (table 1). The populations studied were chosen to complement the existing data set of the worldwide C677T allele frequency. The samples used in this study are anonymous and have been collected for ongoing studies of human genetic diversity. New primers used in this study (forward: 5′-TTT GAG GCT GAC CTG AAG CAC TTG AAG GAG-3′; and reverse: 5′-GAG TGG TAG CCC TGG ATG GGA AAG ATC CCG-3′) gave a PCR product of 173 bp and fragments of 125 and 48 bp after digestion with *Hin*fI.

The MTHFR polymorphism was found in every population tested. Unlike other mutations, such as factor V Leiden (Rees et al. 1995), Δccr5 (Martinson et al. 1997), and the HLA-H C282Y and H63D hemochromatosis mutations (Merryweather-Clarke et al. 1997), which are common only in Europe, the C677T mutation has a relatively high frequency throughout the world.

The prevalence of the C677T mutation is lowest in Africa (6.6%) compared with Europe and Asia, although there are unexpected findings such as 44.9% in an indigenous Brazilian population and 4.5% in a group of Sri Lankans. All of the populations in this study were in Hardy-Weinberg equilibrium.

Both myocardial infarction (Murray and Lopez 1996) and neural tube defects (Sever 1982) are believed to be more prevalent in Europeans than in Africans. In developed countries where most people are of European origin, the incidence of myocardial infarction is >5 times greater than in sub-Saharan Africa, and the prevalence rate for neural tube defects in whites is 1.5 times higher than in blacks in U.S. populations. Although environmental factors and other genetic factors clearly play an important role, the geographical pattern of the C677T allele frequency supports the hypothesis that it is a risk factor for vascular disease and neural tube defects.

The high frequency of the C677T mutation worldwide is surprising if homozygotes have an increased risk of disease. One possible explanation is that either heterozygous or homozygous mutant genotypes may, in certain circumstances, have a selective advantage over normal individuals. Two such theories have been suggested: a decreased risk of C677T homozygotes for colon cancer (Chen et al. 1996) and a beneficial effect to heterozygotes during times of starvation (Engbersen et al. 1995). In the second hypothesis, the thermolabile form of MTHFR is believed to decrease homocysteine remethylation so that the 1-carbon moieties of derivatives remain available for the vital synthesis of purines and thymidine.

The increased incidence of disease caused by the C677T mutation may only have been mildly deleterious to human populations. This could allow the C677T mutation to behave as an effectively neutral polymorphism so that demographic effects such as genetic drift could outweigh slight negative selection. Populations that had high frequencies of the C677T mutation and have been small in the past would be most susceptible to this effect (Thompson and Neel 1997).

Table 1

World Distribution of the MTHFR Mutation

Country	No.	C/C	C/T	T/T	T Allele Frequency (%)	95% Confidence Range (%)
Europe:						
United Kingdom	94	45	42	7	18.6	13.0–25.9
Africa:						
Central African Republic						
Bantu	44	36	8	0	9.1	3.9–17.9
Pygmies	8	7	1	0	6.25	.16–34.8
Gambia	24	21	3	0	6.25	1.29–18.26
Kenya	61	55	6	0	4.9	1.80–10.7
Madagascar	97	84	13	0	6.7	3.6–11.4
Total	234	203	31	0	6.6	4.5–9.4
Middle East:						
Yemen	46	31	14	1	17.4	9.9–28.2
Asia:						
French Polynesia (Chinese ancestry)	64	38	25	1	21.1	13.9–30.7
Hong Kong (Chinese)	47	22	19	6	33.0	22.4–46.8
Maewo, Vanuatu	71	60	10	1	8.5	4.4–14.8
Mongolia	36	13	20	3	36.1	23.6–52.9
Palembang, Indonesia	61	42	18	1	16.4	10.0–25.3
Total	279	175	92	12	20.8	17.2–24.9
Asia Minor:						
Sri Lanka	67	61	6	0	4.5	1.6–9.7
Australasia:						
PNG Highlanders	85	77	8	0	4.7	2.0–9.3
Americas:						
Nu-Chah-Nulth	37	25	10	2	18.9	10.3–31.7
Brazilian Amerindians	39	12	19	8	44.9	31.2–62.4
Total	76	37	29	10	32.2	23.8–42.6
Grand Total	881					

The correlation between the frequency of myocardial infarction and neural tube defects with the allele frequencies presented here is consistent with the hypothesis that the C677T mutation is a risk factor for these diseases. Further study about the genetic, medical, and nutritional factors affecting the MTHFR polymorphism, as well as a better understanding of human demographic history, is needed to explain its high frequency and widespread distribution.

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Mutational Mechanisms for Generating Microsatellite Allele-Frequency Distributions: An Analysis of 4,558 Markers

To the Editor:

Genomewide linkage searches have been facilitated by the development of panels of microsatellite markers that are widely distributed throughout the genome and are highly polymorphic. Population geneticists have investigated mutational mechanisms for generating new microsatellite alleles, considered infinite allele models (Shriver et al. 1993), single-step mutation models (Shriver et al. 1993; Valdes et al. 1993; Di Rienzo et al. 1994; Deka et al. 1995), and multistep mutation models (Di Rienzo et al. 1994; Kimmel and Chakraborty 1996; Chakraborty et al. 1997), and compared theoretical predictions of various parameters such as number of alleles and degree of heterozygosity with real-world observations. These studies have, in general, examined relatively few markers with data derived from several populations. Here we report an analysis of the extensive, publicly available data for the Généthon $(AC)_n$ microsatellite markers (Dib et al. 1996) to investigate (1) the distribution of allele frequencies and (2) the distribution of size differences between alleles, for an idealized microsatellite marker, and to examine the implications of these observations for the underlying mutational model.

The Fondation Jean Dausset–CEPH database (version 8.1) was downloaded from the FTP server (ftp.cephb.fr). Five thousand sixty-three autosomal Généthon $(AC)_n$ microsatellite markers were identified by the nominal prefix "AFM;" 329 markers were eliminated from subsequent analysis, since the difference in size in base pairs between alleles was not an exact multiple of two. The genotypes of 22 unrelated founders of families 1332, 1347, 1362, 1413, and 1416, all of which originate in Utah, were then compiled for subsequent analysis. Markers were grouped by the number of different-sized alleles found in the sample of 44 Utah chromosomes; alleles were then ranked by size (bp) and the mean frequencies of the ranked alleles for 4,558 markers with between 3 and 11 alleles are plotted in figure 1*A*. The frequency distribution traces a distinctive, asymmetrical pattern that follows a function of the number of alleles. As expected, the mode allele lies midway in rank, and its frequency decreases with the total number of alleles. More noteworthy, we observe that the frequency distributions are all positively skewed (coefficients of skewness range from 0.074 to 0.211), the data are significantly different ($P < .01$) from a random sample drawn from a normal distribution using the Kolmogorov test (performed using the SAS UNIVARIATE procedure [SAS Institute 1990]). The frequency distributions for an additional 176 markers with between 12 and 22 different alleles are not shown, because there were insufficient numbers within each size class, leading to excessive variability.

Computer simulation studies were performed to explore plausible mutational mechanisms that underlie the asymmetrical distribution of mean frequencies of the ranked alleles. Models were based on the Fisher-Wright genetic drift model, in which $2N$ chromosomes were sampled with replacement from a diploid population of size N. Mutations at a rate ν were assigned that replace an allele of size S (measured as number of dinucleotides) with a larger or smaller allele. Markers were assumed to be unlinked and in linkage equilibrium. We examined a single-step mutation model (SSMM) in which newly mutated alleles have size $S + 1$ or $S - 1$ with equal probability (i.e., one dinucleotide repeat motif larger or smaller). We also examined multiple-step mutation models (MSMM) in which new alleles have size $S + n$ or