man Genetics and Molecular Biology, Room 1002, Abramson Research Center, The Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, PA 19104. E-mail: budarf@cbil.humgen.upenn.edu

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The Frequency of the Methylenetetrahydrofolate Reductase–Gene Mutation Varies with Age in the Normal Population

To the Editor:

Cardiovascular disease and cerebrovascular disease are second only to cancer as the leading causes of death in Japan, and their mortality rates rise with the age of the population (Health and Welfare Statistics Association 1995). In addition to environmental factors such as smoking, genetic factors are involved in determining an individual's susceptibility to vascular disease. Because low frequency of genetic risk factors for vascular disease could contribute to a population's longevity, the frequency of potentially protective genotypes may be higher in the oldest segment of the population.

For the past decade, mild hyperhomocysteinemia has been recognized as a risk factor for occlusive arterial disease and thrombosis. Methylenetetrahydrofolate reductase (MTHFR) is the key enzyme in the methylation of homocysteine. A homozygous mutation of the MTHFR gene (677C→T; A→V) alters a highly conserved amino acid, resulting in decreased specific MTHFR activity and elevated levels of homocysteine (Frosst et al. 1995). According to a recent report on patients with premature vascular disease, this mutation is associated with a threefold increase in risk for premature cardiovascular disease (Kluijtmans et al. 1996).

Individuals with the homozygous 677C→T mutation have been reported to show increased thermolability of MTHFR (Frosst et al. 1995). One study attributed the abnormal homocysteine metabolism in 28% of the homocysteinemic patients with premature vascular disease to thermolabile MTHFR (Engbersen et al. 1995). Another study indicated that an association between the thermolabile MTHFR defect and coronary artery disease is independent of other known risk factors for coronary artery disease (Kang et al. 1993).

These observations led us to speculate that the MTHFR mutation may be partly responsible for cardiovascular disease, thus decreasing the probability of an individual's reaching old age. To test this hypothesis, we investigated the frequency of the MTHFR mutation in 945 unrelated, healthy subjects 14–99 years old, all Japanese living in a single local area. Information about health condition (e.g., history of hypertension, hyperlipidemia, diabetes mellitus, stroke, and heart disease) was obtained by semistructured interview of 506 subjects who were >60 years old. We assessed blood pressure at rest twice during the interview.

Taking account of the rising rate of mortality due to cardiovascular and cerebrovascular diseases in people >80 years old, we stratified the subjects into three age groups: younger ($\leqslant$54 years; $n = 311$), older (55–79 years; $n = 486$), and oldest ($\geqslant$80 years; $n = 148$, of whom 22 were $\geqslant$90 years of age). DNA was extracted from peripheral leukocytes obtained from each subject, and MTHFR genotyping was performed as described by Frosst et al. (1995).

As shown in table 1, the MTHFR mutation decreased as the ages of the subjects increased. The homozygous MTHFR mutation occurred in 19% of the younger group and in 14% of the older group, whereas we found the mutation in only 7% of the oldest group. The homozygous mutation occurred significantly less often in both the older and oldest groups than in the younger group, especially among males (total—df = 2, $\chi^2 = 10.39$, $P = .006$; males—df = 2, $\chi^2 = 7.25$, $P = .027$; females—df = 2, $\chi^2 = 3.59$, $P = .166$). The MTHFR-genotype distributions for the younger and older age groups were in Hardy-Weinberg equilibrium, but the distribution for octogenarians and nonagenarians was not

Table 1

MTHFR Genotype in Healthy Japanese Stratified by Age Groups and Gender

	Younger (<55 years)			Older (55–79 years)			Oldest ($\geqslant$80 years)		
		MTHFR Allele[a]			MTHFR Allele[a]			MTHFR Allele[a]	
	n	+/+	+/− or −/−	*n*	+/+	+/− or −/−	*n*	+/+	+/− or −/−
Male[b]	147	.21	.79	227	.15	.85	79	.08	.92
Female	164	.17	.83	259	.13	.87	69	.07	.93
Total[c]	311	.19	.81	486	.14	.86	148	.07	.93

[a] A plus sign (+) denotes the mutant allele; and a minus sign (−) denotes the wild-type allele.
[b] $\chi^2 = 7.25$, $P = .027$, for differences among the three age groups.
[c] $\chi^2 = 10.39$, $P = .006$, for differences among the three age groups.

Table 2

Frequency of Hypertension History and Mean Blood Pressure at Rest, among MTHFR Genotypes, Stratified by Age Groups

	MTHFR Allele[a]			
	Older Group (55–79 years)		Oldest Group (⩾80 years)	
	+/+ (n = 57)	+/− or −/− (n = 333)	+/+ (n = 11)	+/− or −/− (n = 107)
No. of individuals with hypertension:				
Present	23 (40.4%)	116 (34.8%)	0[b]	44 (41.1%)
Absent	34 (59.6%)	217 (65.2%)	11 (100%)	63 (58.9%)
Mean (SD) maximum blood pressure at rest (mmHg)	142.5 (35.2)	145.1 (33.4)	147.3 (28.0)	149.9 (30.2)

[a] A plus sign (+) denotes the mutant allele; and a minus sign (−) denotes the wild-type allele.
[b] df = 1, $\chi^2 = 5.56$, $P = .018$, with continuity correction.

(i.e., there was a nonsignificant trend, $\chi^2 = 4.71$, $P < .1$). However, none of the nonagenarians carried the homozygous MTHFR mutation. This finding led us to compare the frequency of past illness and blood pressure among subjects of each age group.

As shown in table 2, there were no significant differences between MTHFR-genotype distribution and the frequency of any past illness (e.g., hypertension, hyperlipidemia, diabetes mellitus, stroke, and heart disease) among the older group, but among the oldest group the frequency of hypertension history was lower among subjects with the homozygous MTHFR mutation. Although this difference was statistically significant according to the χ^2 test with continuity correction, this significance should be interpreted carefully because of the small number of subjects with the homozygous MTHFR mutation.

Our results suggest that the homozygous MTHFR mutation is a genetic factor that prevents the attainment of old age. Moreover, it might indicate that persons who had the homozygous MTHFR mutation, especially those with high blood pressure, could not attain old age. However, the finding, among both old age groups, that there were no blood-pressure differences in subjects with the homozygous MTHFR mutation versus those with other genotypes suggests that some other genetic or environmental factors influence longevity. Because folate supplementation lowers homocysteine concentrations in subjects with hyperhomocysteinemia (Boushey et al. 1995), increased folate intake may promote the longevity of subjects with the homozygous MTHFR mutation. Further investigation, focusing on this mutation and other possible risk factors and on their interaction with other nutritional and genetic factors, as well as the determination of the frequency of the MTHFR mutation in centenarians, is warranted to clarify the association between the MTHFR mutation and longevity.

Sachio Matsushita,[1] Taro Muramatsu,[1] Hiroyuki Arai,[2] Toshifumi Matsui,[2] and Susumu Higuchi[1]

[1]*National Institute on Alcoholism, Kurihama National Hospital, Kanagawa, Japan; and* [2]*Department of Geriatric Medicine, Tohoku University School of Medicine, Sendai, Japan*

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Address for correspondence and reprints: Dr. Sachio Matsushita, Department of Psychiatry, National Institute on Alcoholism, Kurihama National Hospital, 5-3-1 Nobi, Yokosuka, Kanagawa 239, Japan. E-mail: shiguchi@wa2.so-net.or.jp

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