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SHORT REPORT

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Association between the MLH1 gene and longevity

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Abstract Perturbations in genomic stability result in cancer, a reduced life span, and premature aging. MLH1 is a mismatch repair enzyme that acts to maintain genomic stability, and a loss of MLH1 increases cancer incidence and apoptosis resistance, which suggests a link between MLH1 and longevity. We found here that MLH1 is associated with longevity by comparing a centenarian group with a control group. Our data indicate a critical role for MLH1 in longevity.

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Human homolog of the MutL gene of E. *coli*(MLH1), is one of the critical genes that maintain the stability of the genome, and its functional shortcomings are strongly associated with human colon cancer. Loss of the MLH1 gene results in microsatellite instability, which is not only a hallmark of cancer but may be central to the mechanism of cancer development. MLH1-deficient mice are prone to cancer development (Prolla et al. 1998). These phenotypes are similar to those typically encountered in aged humans. In addition, MLH1-deficient cells show resistance to the apoptosis induced by DNA damaging agents, which is consistent with evidence of a decline in apoptotic response during aging (Hardman et al. 2001). Recently, it was demonstrated that mutations throughout the entire coding regions of MLH1 are predominantly inactivating, and thus eliminate the effect of wild-type MLH1 in proliferating cells (Shcherbakova and Kunkel 1999; Pang et al. 1997). Therefore, we hypothesized that polymorphisms of MLH1 influence genomic stability and thereby life span. To examine this hypothesis, we analyzed the entire coding region of the MLH1 gene in 85 Korean centenarians and in 106 Korean controls using two-dimensional gene scanning. Two-dimensional gene scanning (TDGS) is a method of mutation detection based on the electrophoretic separation of PCR-amplified DNA fragments based on size in the first dimension, and on base sequence in the second dimension (Dhanda et al. 1998). We identified nine single nucleotide variants of MLH1 in two population groups, of which we focused on three SNPs in a coding sequence leading to an amino acid substitution because cSNPs play important roles in the function of protein MLH1 (C670T; Arg217Cys, A676G; Ile219Val, T1172A; Val384Asp). The distributions of all three SNPs were in Hardy–Weinberg equilibrium (HWE: $P > 0.05$, data not shown). Analyses of all genotype and haplotype associations with longevity were performed using logistic regression models, after adjusting for the confounding effects of gender caused by differences in ascertainment.

Table 1 Effect of MLH1 haplotype on longevity

	Centenarians		Controls		*P* value	AOR[a]	95% CI
Age	102.33 ± 2.59[b]		56.24 ± 10.67[b]		< 0.0001[c]		
Gender (%)	Male	Female	Male	Female			
	14(16.47)	71(83.53)	49(46.23)	57(53.77)	< 0.0001[d]		
Haplotype[e]							
CAT	13(92.86)	67(94.37)	39(79.59)	47(82.46)	0.0206	3.507	1.213, 10.14
Others	1(7.14)	4(5.63)	10(20.41)	10(17.55)			

[a]AOR: adjusted odds ratio, adjusted for sex
[b]Means and standard deviations
[c]*T* test on the two groups
[d]Chi-squared test on the two groups
[e]Haplotype frequencies and individual haplotypes were generated using the Expectation Maximization (EM) algorithm, which reconstruct individual probabilities for individual phasing accuracy based on unphased genotype data, as well as estimates on the overall haplotype frequencies and their standard errors.

Marginally significant allelic association was detected only between polymorphism at position 1172 and longevity by dominant model ($P = 0.0443$, adjusted odds ratio (AOR) $= 0.199$, 95% confidence interval (CI): 0.041–0.96). According to our hypothesis, we further compared the frequencies of MLH1 haplotypes in the centenarian and control groups under recessive model. In order to avoid misleading results caused by rare haplotypes, we analyzed all haplotypes with a frequency over than or equal to 5% in both the centenarians and the controls, resulting in one major haplotype CAT. We found that the CAT haplotype frequency was significantly higher in the centenarians than in the controls ($P = 0.0206$; Table 1). Moreover, since mutation rate is positively correlated with age, our data show that centenarians have an unexpected MLH1 gene haplotype frequency (Wei 1998).

Cancer is a disease that rises exponentially with age, and as the populations of many countries age, so cancer-related deaths are likely to become even more prevalent in the twenty-first century. However, centenarians have escaped overt cancer. Our data suggest that maintaining genomic stability contributes to longevity, and that DNA repair has a critical role during the aging process.

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