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Trinucleotide Repeat Polymorphisms of Spinal and Bulbar Muscular Atrophy (*SBMA*) Gene in Asian Populations

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I previously reported the PCR-based Spinal and bulbar muscular atrophy (SBMA) region polymorphisms in the three northeast Asian populations (Chinese, Koreans, Japanese) and Caucasians. Here I update this analysis by including the data of the allele distribution in 378 unrelated individuals from four populations in Asia.

In this study I investigated PCR-based CAG repeat polymorphism on the SBMA locus among four Asian populations (Mongolian, Evenki, Orochon, Negrito) and performed the statistical analysis on the eight populations including the previously analyzed data.

Both statistical analyses of one-way ANOVA ($F=3.284$, $P=0.002$) and Kruskal-Wallis test ($\chi^2=21.542$, $DF=7$, $P=0.003$) showed remarkable differences in CAG allele distributions among the populations. Post-hoc test showed that the difference between Negritos and Caucasians was especially significant (Scheffe: $P=0.042$; Bonferroni: $P=0.004$). Also a significant differences among Northeast Asians, Caucasians and Negritos (Southeast Asian) were detected by these two tests (ANOVA; $F=8.132$, $P<0.000$, Kruskal-Wallis; $\chi^2=16.614$, $DF=2$, $P<0.000$). Post-hoc test showed that the differences between Negritos and Caucasias was also especially significant (Scheffe: $P=0.001$; Bonferroni: $P=0.000$) among these three groups.

These data present that the CAG repeat polymorphism of SBMA gene has a useful information for studies of human population genetics.

Key words : Spinal and bulbar muscular atrophy (SBMA), Androgen receptor (AR), CAG trinucleotide repeat polymorphisms, Northeast Asian

Introduction

Among STRs (Short Tandem Repeats) trinucleotide repeats are remarkably investigated because these repeat expansions are related with human neurodegenerative disorder. Until now thirteen such human diseases including myotonic dystrophy (MD) (Brook et al. 1992), fragile X syndrome (FRAXA, FRAXE) (Fu et al. 1991), Huntington's Disease (HD) (The Huntington's Disease Collaborative Research Group 1993), spinal and bulbar muscular atrophy (SBMA) (La Spada et al. 1991), spinocerebellar ataxias (SCA1, 2, 6-8, 12) (Orr et al. 1993, Imbert et al. 1996, Pulst et al. 1996, Sanpei et al. 1996, David et al. 1997, Zhuchenko et al. 1997, Holmes et al. 1999, Koob et al. 1999), Machado-Joseph disease (MJD/SCA3) (Kawaguchi et al. 1994), and Dentatorubral-pallidoluysian atrophy (DRPLA) (Koide et al. 1994) have been investigated. And unaffected normal populations show highly triplet repeat

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polymorphisms on these neurodegenerative disease loci. X-SBMA (X-linked spinal and bulbar muscular atrophy, Kennedy's disease) is characterized by the adult onset of proximal muscle weakness, atrophy, fasciculations, and SBMA patients also show signs of androgen insensitivity such as gynecomastia, deduced fertility and testicular atrophy. Thus it was thought that the *SBMA* gene was related to AR. According to further studies it is known that AR gene is located on Xq11.2-q12, 70～80 kb length including 8 exons and 7 introns (Janne et al. 1991), and the expansion of CAG repeat in exon 1 of the SBMA patients causes this disorder (La Spada et al. 1991). The range of CAG repeat length of SBMA locus in normal individuals is between 11 and 33 CAG repeats, whereas the expanded alleles after 33 repeats cause the SBMA disease (Bates et al. 1994). The repeats lengths of expansion inversely correlated with the age of onset of the disease. (Brooks et al. 1995). Although detailed mechanism of trigerring SBMA onset has not been clarified, recent studies show the possible mechanism of SBMA onset. The polyglutamine expansion causes the AR to lose a function that is necessary for full androgen sensitivity and to gain a function that is selectively toxic to motor neurons (Mhatre et al. 1993). Progressive expansion of the CAG repeat in human AR caused a linear decrease of transactivation function, and importantly, expansion of the tract did not completely eliminate AR activity (Chamberlain et al. 1994). AR N-terminal domain contributes to AR transactivation activity via functional interactions with p160 coactivators and polyQ length negatively affects p160-mediated coactivation of the AR (Irvine et al. 2000). Additionally to this functional alteration, compromising the ubiquitin/proteasome pathway enhances degeneration and decreases poly(Q) protein solubility. Post-translational protein modification, including the ubiquitin/proteasome and the SUMO-1 pathways, modulate poly(Q) pathogenesis (Bailey et al. 2002, Chan et al. 2002). They demonstrated that molecular chaperone-enhancement of protein degradation points to the modulation of molecular chaperones as a potential therapeutic target for polyglutamine diseases. However the mechanism for the abarrently accumulated expanded polyglutamine to induce the neuronal dysfunction is not elucidated clearly.

And interestingly unaffected populations show highly CAG repeat polymorphisms on this SBMA locus. Although the phenomena of CAG repeat expansion in SBMA locus had been reported at relatively early time, there have been few polymorphism studies in Asian ethnic populations. The analysis of the different distribution of these repeat sequences among normal populations is very important not only to the better understanding of human population structure but also to the determination of the baseline data for medical sciences. Therefore in this report I investigated the PCR-based STRs polymorphisms on SBMA locus for Mongolian, Evenki, Orochon, and Negrito samples. Distributive differences among them and other populations reported in our previous study were analyzed using ANOVA and Kruskal-Wallis test.

Materials and Methods

1. Blood samples and DNA preparation

166 unaffected Mongolians of Outer Mongolia (Khalha ethnic group), 112 Evenki and 80 Orochons of Inner Mongolia as Northeast Asian ethnics, and 20 Philippine Negritos of west-central Luzon (Aeta ethnic group) as one of Southeast Asian populations were examined. Negritos are characterized by small stature, dark skin, frizzy hair, a projecting jaw and a broad nose. They are forest dwellers, usually living in isolated regions scattered throughout Southeast Asia. They may be descendants of some of the earliest immigrants in Southeast Asia, who were once much more widespread and their precise genetic origins are poorly understood. Evenki and Orochon people, living in the

northern part of The Inner Mongolia Autonomous Region in China were studied. The Evenki people are scattered over vast parts of Siberia and northern China. They belong to the indigenous peoples living in the Taiga regions of North and Northeast Asia. The Orochon people are closely related to the Evenki people living in northern China. DNA samples were obtained from the buffy coat of peripheral blood or lymphoblastoid cells by using the standard DNA extraction method of Sambrook et al. (1989). All samples were obtained with appropriate informed consent.

2. PCR and electrophoresis

DNA amplification by PCR was performed using previously reported primers (La Spada et al. 1991), modified by labeling the 5′ end of SBMA with phosphoramidites (HEX) (Applied Biosystems). The PCR and electrophoresis was performed with the same condition of Lee et al. (1997).

3. Semi-automatic DNA size definition and statistical analysis

Allele sizes were determined by coelectophoresis of the size standard and PCR product of the sequenced plasmid DNA (pvsARO). PvsARO is a subcloned DNA of a SBMA patient. The sequence of pvsARO is a form of CTG $(CAG)_{19}$CAA (Faber et al. 1989). Analysis was performed using the GENESCAN^{TM} 672 (Version 1.2) software (ABI) installed in a 373A Sequencer. The automatically estimated result file was imported into the Genotyper^{TM} (Ver.1.0, ABI) and the sample alleles were determined and tabulated. The final data were stored in Excel (Ver.5.0) for statistical analyses and then allele frequencies and heterozygosity were calculated. Heterozygosity was estimated according to the following formula: heterozygosity$=1-\sum\chi_i^2 \cdot \chi_i$ is observed frequency of each allele size. To estimate the difference of distribution among populations including our published data, both of One-way ANOVA and Kruskal-Wallis test were performed using SPSS (Version 10.0) package programs. I performed Scheffe and Bonferroni test as post-hoc tests among populations.

Results

The allele distributions of every population are shown in Table 1. Totally 1146 alleles which are located in X chromosomes were compared. CAG allele that marked the highest frequency was 22 repeats in Evenki and Negrito, while in Mongolian it was 23 repeats. In Orochon, the most frequent CAG allele was 25 repeats (Fig. 1 and Table 1). The means of CAG lengths in Mongolian, Evenki, Orochon, and Negrito were 22.97 $\pm$3.34, 22.89$\pm$2.92, 23.29$\pm$2.61, and 24.6$\pm$3.07, respectively (Table 1). Our previously reported data of Chinese, Korean, Japanese and, Caucasian were compared with these results. Allele distribution of Mongolian was typical unimodal like the ones of Chinese and Korean. The range of heterozygosity of these populations was 0.82$\sim$0.9. As shown in Table 1 the heterozygosities of Evenki and Orochon were comparatively high among Northeast Asian populations. The ones of Northeast Asians and Caucasians were equal (0.89). Negrito's heterozygosity was the lowest (0.82). While the mean length of alleles in Negrito (24.6$\pm$3.07) was the highest among every population, the mean of Caucasians (22.32$\pm$3.21) was the lowest. According to the ANOVA test among all populations including our published data (Lee et al. 1997), significant differences ($F=3.284$, $P=0.002$) were depicted. Kruskal-Wallis test also showed differences ($\chi^2=21.542$, DF$=$7, $P=0.003$). Post-hoc test showed that the differences between Negritos and Caucasians were especially significant (Scheffe: $P=0.042$; Bonferroni: $P=0.004$). After grouping these populations to Northeast Asians, Caucasians and Negritos (Southeast Asian), differences among these three groups were examined also using these two tests. The result presented significant differ-

Table 1. Distribution of the CAG Repeats in the *SBMA* locus among the unaffected populations

No. of CAG repeats	Mongolian	Evenki	Orochon	*Chinese	*Japanese	*Korean	Northeast Asian	*Caucasian	Negrito
9	1	0	0	0	0	0	1	0	0
10	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	1	0
12	0	0	0	0	1	1	2	0	0
13	0	0	0	0	0	1	1	0	0
14	2	1	0	0	0	0	3	0	0
15	1	1	0	0	0	0	2	2	0
16	3	3	0	0	1	0	7	1	0
17	2	1	0	0	3	0	6	0	0
18	4	4	11	1	1	5	26	1	0
19	5	9	6	5	7	11	43	13	0
20	12	19	5	8	10	9	63	15	0
21	27	18	7	13	16	14	95	16	0
22	26	30	18	35	17	37	163	16	10
23	28	23	23	31	31	32	168	20	6
24	27	20	22	16	12	23	120	10	4
25	19	28	27	14	11	17	116	7	2
26	12	9	9	10	18	12	70	8	5
27	10	9	2	5	5	11	42	3	0
28	3	5	1	9	1	9	28	1	0
29	3	4	1	4	0	5	17	2	2
30	1	2	3	2	0	3	11	0	1
31	2	0	0	2	1	0	5	1	1
32	0	0	0	0	0	1	1	1	0
33	0	0	0	0	0	0	0	1	0
34	0	0	2	0	1	0	3	0	1
35	1	0	0	0	0	0	1	0	0
36	1	0	0	0	0	0	1	0	0
Total	190	186	137	155	136	191	995	119	32
Hterozygosity	0.9	0.9	0.87	0.87	0.87	0.89	0.89	0.89	0.82
Length (M±SD)	22.97±3.34	22.89±2.92	23.29± 2.61	23.54±2.62	22.89±2.85	23.32±2.98	23.14±2.97	22.32±3.21	24.6±3.07

*: Reported data in Lee et al. (1997); Northeast Asian: Mongolian, Evenki, Orochon, Chinese, Korean, Japanese.
Total: total chromosomes analyzed; ML: mean length; M: mean; SD: standard deviation.

ences (ANOVA; F=8.132, $P<0.000$, Kruskal-Wallis; $\chi^2=16.614$, DF =2, $P<0.000$). Post-hoc test showed that the differences between Negritos and Caucasias was also especially significant (Scheffe: $P=0.001$; Bonferroni: $P=0.000$) among these three groups.

Discussion

Notwithstanding that this SBMA locus is polymorphic among populations, the population studies in this locus were limited except for several reports (Watkins et al. 1995, Arrieta et al. 1997, Gyürüs et al. 1999). The present study is focused on the Asian populations. Negrito showed a remarkable upper quartile shape; this distribution represents that Negrito is genetically unique when we consider that this upper qurtile shape was not detected in other populations such as Africans (Watkins et al. 1995; lower quartile shape; the prominent repeat allele was 18), other Asians (Korean, Chinese, Japanese), Caucasians (Lee et al. 1997), and Hungarians (Gyürüs et al. 1999). Heterozygosity of

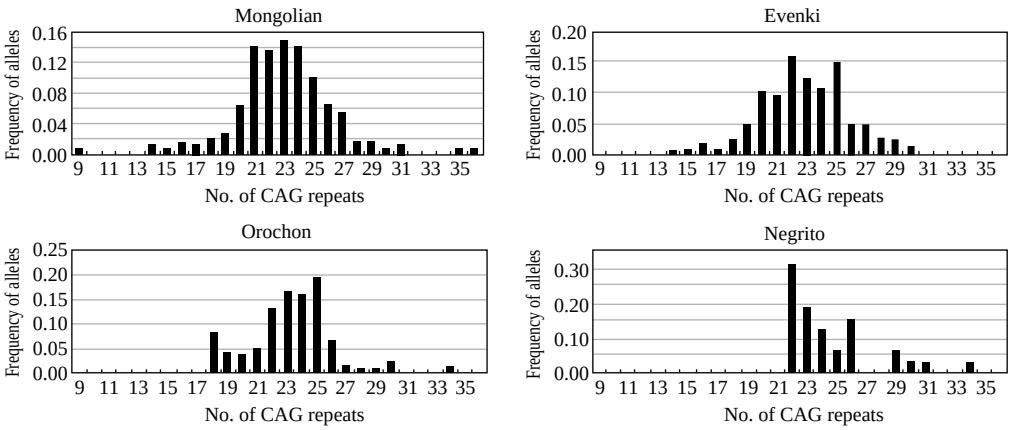

Fig. 1. Allele size distributions of the CAG repeats in SBMA locus of unaffected samples of Mongolian, Orochon, Evenki, and Negrito.

Table 2. Heterozygosities of eight populations on the four loci

	Mongolian	Chinese	Evenki	Orochon	Korean	Japanese	Negrito	Caucasian
HD	0.67	0.61	0.72	0.71	0.59	0.6	0.57	0.8
MJD	0.8	0.7	0.83	0.89	0.78	0.78	0.71	0.79
SCA1	0.78	0.78	0.79	0.78	0.79	0.77	0.77	0.73
SBMA	0.9	0.87	0.9	0.87	0.89	0.87	0.82	0.89

Negritos was relatively low (0.82) comparing to the report of Watkins (1995) (Asians: 0.88, Africans: 0.9, Caucasians: 0.89) However Hungarian population significantly showed the lowest heterozygosities (0.60) among the populations which were previously reported and were investigated in this study. It was also the lowest among the investigated 4 loci (HD, DRPLA, SBMA, and SCA1) except DM locus (Gyürüs et al. 1999).

Particularly in this analysis of SBMA locus every population showed relatively high heterozygosities compared to the ones of CAG repeats for HD, SCA1, and MJD loci (Table 2) of our data in these populations. This is concordant with the results reported by Watkins et al. (1995). The high heterozygosity of SBMA locus may indicate that the SBMA gene had the possibility to exchange genes with various populations more widespreadly than the other three loci.

The range of CAG repeat length of SBMA locus in normal individuals and patients is various according to the population, Mohmood reported that the normal range is 9～36 and that the expanded one is 38～65. In the present study of normal populations the novel CAG alleles of 9, 35, 36 (Mongolian), 14 (Evenki and Mongolian) were detected.

In addition the polymorphic CAG repeat, another triplet repeat, (GGC)n is located approximately 1.2 kb downstream from the (CAG)n in the first exon of the AR gene (Sleddens et al. 1993). In SBMA patients of Japanese and Scandinavian linkage disequilibrium was found between the CAG repeat expansion and the GGC repeat, indicating a founder effects (Tanaka et al. 1996, Lund et al. 2000). Founder effect has also been reported in SCA1 (Wakisaka et al. 1995), SCA2 (Hernandez et al. 1995) and SCA3 (Machado-Joseph disease) (Mizushima et al. 1999). The distribution of the

GGC repeats on SBMA locus significantly differs among the various racial-ethnic control subjects (Irvine et al. 1995). They reported that 70% of Asian controls (Chinese and Japanese which were residing in Los Angeles County) had $(GGC)_{16}$ compared to 57% Caucasian and 20% African-American controls, and very few Asians (3%) had alleles longer than 16 which otherwise were common in Caucasians (32%) (Irvine et al. 1995). In this report we performed the analysis of the differences of CAG repeat on SBMA locus among populations, and further study of the GGC repeat polymorphism should be continued for a detail understanding the genetic association among populations.

Conclusively our data showed that CAG repeat polymorphism of *SBMA* gene has a useful information for studies of human population genetics.

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아시아 집단에 있어서의 *SBMA* 유전자 좌위의 CAG 3염기 반복배열의 다형성 분석

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간추림 : 연구자는 이전에 PCR 기법을 이용하여 Spinal and bulbar muscular atrophy (*SBMA*) 유전자의 CAG 3 염기 반복의 다형성이 중국인, 한국인, 일본인과 코카소이드 집단사이에 존재한다고 보고한 바 있다. 본 연구에서 네 개의 아시아 민족(몽골인, Evenki 인, Orochon 인, 필리핀 Negrito) 378 인의 DNA 샘플에 대한 대립유전자 데이터를 첨가하고 이전발표 데이터와 종합하여 이들 대립유전자의 집단간 분포를 분석하였다.

PCR 기법을 이용하여 네 아시아 집단(몽골인, Evenki인, Orochon인, Negrito인)에 대하여 SBMA좌위의 CAG 반복배열의 다형성을 조사하고 이전 보고한 데이터와 통합하여 통계분석을 하였다.

통계분석을 적용한 결과 대립유전자들은 이들 8개 집단 간 유의적인 차이를 보이며 분포하고 있었고 특히 ANOVA 테스트의 결과에 대한 사후 검정 결과 Negrito와 코카소이드 집단간의 차이가 유의적으로 컸다(Scheffe: P=0.042; Bonferroni: P=0.004).

SBMA 유전자내의 CAG 3염기 반복배열의 다형성은 인류의 집단유전학 연구에 있어서 유용한 정보를 제시한다고 하겠다.

찾아보기 낱말 : spinal and bulbar muscular atrophy (SBMA), 안드로젠 수용체, CAG 3 염기 반복 다형성, 동북아시아인, negrito

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