Distribution of Group-Specific Component/Vitamin D-Binding Protein Alleles in Southwestern Japan and Geographical Clines of Allele Frequencies in Japanese Populations

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Abstract To scrutinize the geographical clines of allele frequencies of the group-specific component/vitamin-D binding protein (GC) system in Japan, the GC types in nine populations of southwestern Japan including Okinawa were determined. The frequencies of the common alleles in the island populations, especially, Yakushima and Miyako were found to be scattered more extensively than those in the populations of the mainland Japan. GC*1A2 was polymorphic in all populations except in the southwesternmost islands, Miyako and Ishigaki. The geographical clines of GC*1F, GC*1S and GC*2 frequencies are discussed in connection with the migration of the Yayoi era.

Keywords: Genetic polymorphism, Geographical cline, Group-specific component, Japanese population, vitamin D-binding protein

Introduction

Group-specific component (GC), a plasma protein, is currently called vitamin D-binding protein (DBP) after its function (Daiger and others, 1975). However, GC/DBP not only act as a carrier of vitamin D but also has some functions (Constans, 1992). The genetic polymorphism of the human GC/DBP system was first shown to be controlled by GC*1 and GC*2 by Hirschfeld (1959) using immunoelectrophoresis. Since Constans and Viau (1977), using isoelectric focusing (IEF), divided GC*1 into GC*1F and GC*1S, more than 120 variant alleles have been observed at the GC locus on chromosome 4 (Cleve and Constans, 1988). The population distribution of three common alleles, GC*1F, GC*1S and GC*2 and some variant alleles have been studied to elucidate human microevolutions (Constans and others, 1985).

Geographical clines of allele frequencies are useful to consider historical events, migration and natural selection. Some geographical clines associated with migration have been recognized in Japanese populations (Ishimoto and Kuwata, 1974; Fujita and others,

1978; Ueda and others, 1979; Yuasa and others, 1983a, 1983b; Omoto, 1986; Nakanaga and others, 1991). Recently, we examined the clines arising from the differences in TF allele frequencies between the aboriginal people of the Jomon era and the immigrants from north Asia in the Yayoi era using data from the Nansei Islands (Ago and others, 1998). The Nansei Islands which comprise the Satsunan Islands and the Ryukyu Islands consist of many islands scattered like a longbow between mainland Kagoshima Prefecture in Japan and Taiwan (Ago and others, 1998). Jomon characteristics remain more noticeable in the peripheral populations of the Nansei Islands than in the mainlanders, since the Yayoi immigrants came mainly to the western part of the mainland Japan from or through the Korean Peninsula. Thus the Nansei Islands are important in tracing the origins of the Japanese people (Hanihara, 1991). To scrutinize the geographical clines in Japan, in this paper, we investigate the distribution of GC allele frequencies in the populations of the Nansei Islands.

Materials and Methods

Serum samples were obtained from blood donors living in nine regions as shown in Table 1. One region is mainland Kagoshima Prefecture, and the remaining eight are islands: Tanegashima, Yakushima, Amami-oshima, Tokunoshima and Okinoerabu in the Satsunan Islands, and Okinawa, Miyako and Ishigaki in the Ryukyu Islands.

GC phenotyping was carried out by IEF on acrylamide gel containing Pharmalyte pH 4.5-5.4 (Pharmacia, Uppsala, Sweden) followed by immunoprinting or immunoblotting with monospecific anti-GC serum (Dako, Glostrup, Denmark).

The geographical clines for the frequencies of common GC alleles in Japanese populations were examined as described previously (Ago and others, 1998). In brief, simple linear regression between allele frequencies and distances was statistically tested at the 5% level. The distances were measured along railroads and sea routes from Aomori, Osaka and Yamaguchi to the investigated districts.

Table 1 GC allele frequencies in the populations of the Nansei Islands and mainland Kagoshima Prefecture

Populations	n	Frequencies									
		GC*1F	GC*1S	GC*2	GC*1A2	GC*1A3	GC*1A8	GC*1A9	GC*1C2	GC*1C4	GC*1C35
Mainland	349	0.4628	0.2335	0.2851	0.0115	0.0029	-	0.0043	-	-	-
Tanegashima	320	0.4859	0.1891	0.3047	0.0172	0.0016	-	0.0016	-	-	-
Yakushima	365	0.4411	0.2753	0.2671	0.0110	0.0014	-	0.0014	0.0014	0.0014	-
Amami-oshima	370	0.4297	0.1959	0.3459	0.0176	-	0.0014	0.0068	-	0.0027	-
Tokunoshima	280	0.4732	0.1893	0.3179	0.0125	0.0018	-	0.0036	-	0.0018	-
Okinoerabu	371	0.4636	0.2426	0.2695	0.0175	0.0013	-	0.0027	-	0.0027	-
Okinawa	362	0.4461	0.2099	0.3149	0.0193	0.0014	0.0014	0.0055	-	-	0.0014
Miyako	350	0.5514	0.1729	0.2643	0.0086	-	-	-	0.0014	0.0014	-
Ishigaki	332	0.4864	0.2018	0.3012	0.0075	-	-	0.0030	-	-	-

Results

Six common and 16 variant phenotypes were observed. A homozygote of GC*1A2 was observed in Tanegashima and Okinoerabu, and a rare heterozygous phenotype GC1A3-1A9, in mainland Kagoshima. In all the populations except Okinoerabu the observed numbers were in agreement with expectations assuming Hardy-Weinberg equilibrium ($p > 0.05$). As shown in Table 1, the frequencies of common alleles were: 0.4297-0.5514 for GC*1F, 0.1729-0.2753 for GC*1S and 0.2643-0.3459 for GC*2. The chi-square test using the frequencies of GC*1F, GC*1S and GC*2 at the 5% level showed that Yakushima and Miyako (especially Yakushima) significantly differed from other populations. However, Yakushima was not significantly different from mainland Kagoshima. Of several rare variants observed, GC*1A2 was the most common in all populations and polymorphic (> 0.01) except in Miyako and Ishigaki.

The geographical clines of GC allele frequencies in Japanese populations were examined using the present and previous data, as shown in Table 2. As described in the analysis of clines in the TF system (Ago and others, 1998), three localities were examined as the origin of the clines. Firstly, as in previous studies (Yuasa and others, 1983a, 1983b; Omoto, 1986) clines were examined by measuring distances from Aomori. The distribution patterns of the allele frequencies are shown in Figure 1. There were statistically significant clines increasing in frequency for GC*2 ($y = 0.0183x + 0.2469$, $R = 0.73$, $F = 32.8$, $n = 31$, $P < 0.001$) and decreasing for GC*1S ($y = -0.0173x + 0.2646$, $R = 0.66$, $F = 22.4$, $n = 31$, $P < 0.001$) from Aomori to Ishigaki, but not for GC*1F.

Table 2 Distribution of GC allele frequencies in populations throughout Japan

Populations	n	Frequencies			Distance (Km) from			References
		GC*1F	GC*1S	GC*2	Aomori	Osaka	Yamaguchi	
Aomori	593	0.4545	0.2470	0.2664	0	-1296	-1779	Yoshioka and others, 1984
Akita	732	0.4693	0.2473	0.2582	186	-1128	-1611	Shindo and Takahashi, 1983
Iwate	697	0.4699	0.2461	0.2518	204	-1092	-1575	Yoshioka and others, 1984
Iwate	500	0.480	0.238	0.242	204	-1092	-1575	Omoto, 1986
Miyagi	647	0.4359	0.2666	0.2589	387	-908	-1392	Yoshioka and others, 1984
Yamagata	689	0.4347	0.2612	0.2663	450	-916	-1400	Umetsu and others, 1985
Fukushima	893	0.4854	0.2402	0.2469	466	-829	-1313	Abe, 1983
Tokyo	305	0.4656	0.2590	0.2574	739	-556	-1040	Omoto and Miyake, 1978
Tokyo	531	0.487	0.241	0.246	739	-556	-1040	Ishimoto and others, 1979
Tokyo	526	0.4695	0.2610	0.2438	739	-556	-1040	Nakajima and Nakazawa, 1980
Yamanashi	530	0.4642	0.2557	0.2547	873	-499	-982	Kido and others, 1984
Toyama	1047	0.429	0.255	0.282	696	-327	-810	Ohya and others, 1986
Mie	510	0.465	0.241	0.263	1149	-127	-610	Ishimoto and others, 1979
Osaka	316	0.4209	0.3006	0.2579	1296	0	-483	Matsumoto and others, 1979
Osaka	342	0.456	0.258	0.254	1296	0	-483	Shibata, 1983
Hyogo								
Awajishima	218	0.4633	0.2454	0.2546	1355	60	-438	Fukui and others, 1993

Table 2. continued

Populations	n	Frequencies			Distance (Km) from			References
		GC*1F	GC*1S	GC*2	Aomori	Osaka	Yamaguchi	
Kochi	1460	0.4527	0.2370	0.2836	1651	356	-486	Ishizu and others, 1986
Shimane								
Izumo	600	0.4524	0.2462	0.2780	1605	378	-244	Yuasa and others, 1984
Yamaguchi	400	0.4422	0.2450	0.2802	1779	483	0	Yuasa and others, 1984
Nagasaki	1058	0.4409	0.2356	0.2909	2069	773	316	Nakasono and others, 1983
Kagoshima								
Mainland	349	0.4628	0.2335	0.2851	2235	940	482	Present study
Tanegashima	320	0.4859	0.1891	0.3047	2350	1055	597	Present study
Yakushima	365	0.4411	0.2753	0.2671	2370	1075	617	Present study
Amami-oshima	370	0.4297	0.1959	0.3459	2618	1323	865	Present study
Tokunoshima	280	0.4732	0.1893	0.3179	2727	1432	974	Present study
Okinoerabu	371	0.4636	0.2426	0.2695	2881	1486	1028	Present study
Okinawa								
Okinawa	502	0.4731	0.2092	0.3157	2968	1673	1215	Matsumoto and others, 1980
Okinawa	397	0.4332	0.2141	0.3212	2968	1673	1215	Yuasa, 1987
Okinawa	362	0.4461	0.2099	0.3149	2968	1673	1215	Present study
Miyako	350	0.5514	0.1729	0.2643	3298	2003	1545	Present study
Ishigaki	332	0.4864	0.2018	0.3012	3409	2114	1656	Present study

Secondly, the clines were separately examined in two parts, eastern (Aomori - Yamaguchi) and western (Yamaguchi - Ishigaki) Japan. As shown in Figure 2, GC*1F and GC*1S frequencies were distributed in a V shape and in an inverted V shape, respectively. The slopes of the clines differed in directionality between the eastern and the western groups. The frequencies of GC*2 were lineally distributed. Significant clines were observed for GC*1S frequencies ($y = -0.0337x + 0.2469$, $R = 0.572$, $F = 5.35$, $n = 13$, $P = 0.041$) in western Japan and for GC*2 frequencies ($y = 0.0119x + 0.2717$, $R = 0.481$, $F = 5.11$, $n = 19$, $P = 0.037$) in eastern Japan. Thirdly, as shown in Figure 3, the origin was shifted to Osaka. In GC*1F and GC*1S frequencies, the V shape and the inverted V shape observed in Figure 2 became more noticeable. The frequencies of GC*2 were lineally distributed, but the slopes of the two lines in northern and western Japan were slightly different. Significant clines were observed in the western group, where frequencies of GC*1F increased ($y = 0.0201x + 0.4391$, $R = 0.47$, $F = 4.6$, $n = 18$, $P = 0.047$), those of GC*1S decreased ($y = -0.0349x + 0.2637$, $R = 0.74$, $F = 18.8$, $n = 18$, $P < 0.001$) and those of GC*2 increased ($y = 0.0221x + 0.2666$, $R = 0.57$, $F = 7.9$, $n = 18$, $P = 0.013$) from northeast to southwest.

Figure 1 Scatter diagrams and clines of GC allele frequencies in Japanese populations. Dotted line indicates that the cline is not significant at the 5% level.

Figure 2 Rearranged scatter diagrams and clines of GC allele frequencies in Japanese populations (1). The dotted line indicates that the cline is not significant at the 5% level.

Figure 3 Rearranged scatter diagrams and clines of GC allele frequencies in Japanese populations (2). The dotted line indicates that the cline is not significant at the 5% level.

Discussion

The frequencies of common GC alleles in the present populations scattered variably in comparison with those in the mainland Japan, as shown in Table 2 and Figure 1. This may be attributed to the isolation of each island. There was a significant difference in the distribution of allele frequencies between Yakushima and Tanegashima, although they are the closest among the localities investigated in the present study (only about 18 Km from each other). In contrast, no significant difference was observed between Yakushima and mainland Kagoshima. Yakushima was governed by the feudal lords of mainland Kagoshima for about 300 years since 1595 A.D., but Tanegashima kept its independence during this period. These historical differences may have affected the frequencies of the GC alleles. The difference between these two islands is also observed in the alpha 1-antitrypsin system (Ago and Tsuganezawa, 1989). GC*1A2, originally reported as GC*Japan (Omoto and others, 1972), was polymorphic in the populations except in Miyako and Ishigaki, the southwesternmost part (Table 1). It is also a genetic marker for the east Asian populations (Kamboh and Ferrell, 1986; Cleve and Constans, 1988). Its frequency in Japanese populations is much higher than in Chinese populations (Zeng and Omoto, 1987; Xu and others, 1989; Yiping and others, 1992; Umetsu and others, 1992).

Yuasa and others (1983a), using 12 data obtained by immunoelectrophoresis, first reported the geographical cline of GC allele frequency in Japanese populations, where

GC*2 frequency increases from north to south between Aomori and Miyazaki. Using 13 data obtained by IEF, Yuasa and others (1983b) confirmed the cline of GC*2 frequencies between Yamagata and Okinawa. Omoto (1986) reported a similar cline between Akita and Nagasaki. The present data supplemented with previous data covered the whole of Japan except Hokkaido, the northernmost part (Table 2). Our first analysis of geographical clines followed the method of previous studies (Yuasa and others, 1983a, 1983b; Omoto, 1986). We found that GC*2 frequency increases from northeast to southwest between Aomori and Ishigaki. In contrast, GC*1S frequency decreases in the same area (Figure 1).

Hanihara (1991), on the formation of the Japanese people, described that the modern Japanese population consists of the three main populations, Hondo Japanese inhabiting mainland Japan, Ryukyans in Okinawa and Ainu in Hokkaido. These populations commonly originate from the Jomonese of the Neolithic Jomon era (12,000 - 2,300 years ago). Later, migration from northeast Asia took place in and after the Aeneolithic Yayoi era (300 B.C. - 300 A.D.). The immigrants mainly came to the northern part of Kyushu and Yamaguchi from or through the Korean Peninsula, and mixed with Hondo Japanese. This population intermixture is still going on. The habitat of the migrants extended from the north part of Kyushu and Yamaguchi to the Kinki district in the early stage (Aoki and Omoto, 1980; Hanihara, 1991; Aoki, 1994). Therefore, we divided the populations into eastern and western groups with borders at Yamaguchi and at Osaka, and reexamined the clines in each group (Figures 2 and 3). The clines for the frequencies of GC*1F and GC*1S had different directivity between the eastern and the western groups, and showed V and inverted V shapes on scatter diagrams. These features suggest that the clines were formed by the migration of populations with different allele frequencies in the Yayoi era. The clines bordered at Yamaguchi were similar to those bordered at Osaka. This suggests that populations between Yamaguchi and the Kinki district are genetically homogeneous.

The distribution profiles of GC*2 frequencies were different from those of GC*1F and GC*1S. The clines for GC*2 in the eastern and western parts have the same directivity increasing from northeast to southwest. GC*2 frequencies were not remarkably affected by the Yayoi immigrants. The cline of GC*2 frequencies suggests that the north-south differentiation among the aboriginal people had been formed before the Yayoi migration started, and that the immigrant population had a frequency intermediate between the frequencies of the northern and southern aboriginal people. Thus, the analysis of clines after the division into eastern and western populations is useful to investigate the historical changes of allele frequency distribution.

The data of Ainu populations, GC*1F = 0.5214, GC*1S = 0.2571, GC*2 = 0.2214 (Omoto and Miyake, 1979) and GC*1F = 0.5793, GC*1S = 0.2030, GC*2 = 0.2085 (Matsumoto and others, 1980), fit the frequencies expected from the distribution profiles of GC alleles in the other Japanese populations.

On the other hand, Mourant and others (1976) made a world map of GC*2 allele frequencies, and showed that high frequencies of GC*2 correspond to low levels of

sunlight with some exceptions. They discussed the results in relation to natural selection and the incidence of rickets, due to vitamin D deficiency. The cline of GC*2 frequencies in Japanese populations, however, is not explicable by natural selection because the frequencies increase from north to south, as indicated by Yuasa and others (1983a). Our previous study on the TF system (Ago and others, 1998) showed that the clines for the frequencies of TF*C1 and TF*C2 have different directivity between the eastern and the western groups bordered at the western part of Honshu, the main island, like those of GC*1F and GC*1S. The findings that similar clines were observed in different systems strongly suggest that the clines were formed by gene flow due to migration, not by natural selection.

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