GENETIC POLYMORPHISMS OF HUMAN COMPLEMENT COMPONENTS BF AND C2 IN KOREAN: POPULATION AND ASSOCIATION STUDIES

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Summary Polymorphisms of the factor B and the second component of human complement were investigated in 220 unrelated healthy Koreans. In the BF system, three phenotypes, S, FS, and F, were observed, while no rare variants were detected. The estimated allele frequencies for *BF*S* and *BF*F* were 0.775 and 0.225 respectively. In the C2 system, one common phenotype, C, and three heterozygous types, BC, BHC, and ATC, were observed. The estimated allele frequencies for *C2*C*, *C2*B*, *C2*BH*, and *C2*AT* were 0.961, 0.018, 0.011, and 0.009, respectively. Significant positive association between *C2*AT* and *BF*F* was found. Gene frequencies in Korean were compared with those in other populations.

INTRODUCTION

Factor B (BF) is one of the major participants in the alternative pathway of complement activation. The second component of human complement (C2) is an early component of the classical complement pathway. BF and C2 are single chain glycoproteins which take part in formation of the C3 and C5 convertases.

The genes for three components of the complement system, C2, C4, and BF, have been localized between HLA-B and HLA-D in the major histocompatibility complex (MHC) of human chromosome 6 (Weitkamp and Lamm, 1982). Recently, these genes were mapped precisely using DNA walking analyses (Carroll *et al.*, 1984).

Genetic polymorphism of human BF protein was discovered by Alper *et al.* (1972) using high voltage agarose gel electrophoresis followed by immunofixation. BF polymorphism has been investigated in many populations and shown to be controlled by codominant alleles at a single structural locus. Two common (*BF*S* and *BF*F*) and several uncommon variants have been identified and designated according to their relative electrophoretic mobilities (Mauff *et al.*, 1978). These

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variants have been useful markers for association analyses with disease susceptibilities (for review, see Rittner and Bertrams, 1981), parentage testings, and population researches.

Genetic polymorphism of human C2 protein was first described by Hobart and Lachmann (1976), Alper (1976), and Meo *et al.* (1977) using isoelectric focusing followed by specific hemolytic overlay. C2 polymorphism is controlled by codominant alleles at a single structural locus. A common allele, $C2^*C$ ($=C2^*I$), a basic variant, $C2^*B$ ($=C2^*2$), and two rare acidic variants, $C2^*A1$ and $C2^*A2$, have been reported in Caucasoid populations (Pariser *et al.*, 1978). In addition, an acidic variant, $C2^*AT$, and two rare basic variants, $C2^*BH$ and $C2^*BJ$, have been observed in Japanese (Tokunaga *et al.*, 1981, 1982b, 1983).

The present paper demonstrates the results of population studies on BF and C2 polymorphisms and analyses on association between BF and C2 alleles in Korean. Also the gene frequencies estimated in Korean are compared with those reported in other populations.

MATERIALS AND METHODS

A total of 220 ACD-plasma samples were obtained from unrelated healthy Koreans living in Seoul, Korea. The samples were stored at -30°C for up to a few months before typing.

Phenotyping of BF was performed by immunofixation electrophoresis in agarose gel as described previously (Tokunaga *et al.*, 1982a). Phenotyping of C2 was performed using isoelectric focusing in polyacrylamide gel and a specific hemolytic detection as described previously (Tokunaga *et al.*, 1980), except that the thickness of the focusing gel was 0.5 mm.

Association between BF and C2 alleles was analyzed in 2×2 contingency tables by Fischer's exact test.

RESULTS AND DISCUSSION

The results of BF typing of 220 unrelated healthy Koreans are presented in Table 1. The allele frequencies estimated for BF^*S and BF^*F were 0.775 and 0.225, respectively. The deviation of the observed numbers of phenotypes from those expected on the Hardy-Weinberg equilibrium was statistically non-significant ($\chi^2=2.234$, 1 d.f., $0.20 > p > 0.10$). Table 2 shows BF allele frequencies in various populations. Variant alleles have been found at considerably low frequencies in Mongoloid populations. No rare phenotypes were observed in the present study. On the other hand, two relatively uncommon alleles, BF^*F1 and BF^*SO7 ($=S1$), are known in Caucasoid and Negroid populations.

The frequencies of BF^*S and BF^*F in Koreans are similar to those reported in other Eastern Asians and Europeans, but differed markedly from those in Negroids.

Table 1. Distribution of BF phenotype and allele frequencies in Korean.

Phenotype	Obs. No.	(%)	Exp. No.	Allele frequency
S	136	(61.8)	132.1	
FS	69	(31.4)	76.7	$BF^*S: 0.775 \pm 0.020$
F	15	(6.8)	11.1	$BF^*F: 0.225 \pm 0.020$
Total	220	(100.0)	219.9	1.000

$\chi^2=2.23$, 1 d.f., $0.2 > p > 0.1$.

Table 2. Distribution of BF allele frequencies in various populations.

Population	No.	BF allele					Authors
		S	F	F1	SO7	Others	
Korea	220	.775	.225	0	0	0	Present study
Japan	360	.824	.176	0	0	0	Horai, 1976
Japan	487	.801	.198	0	0	.001	Tokunaga <i>et al.</i> , 1982a
China	200	.870	.127	0	.003	0	Tongmao, 1983
Thailand	184	.902	.098	0	0	0	Greiner <i>et al.</i> , 1980
India	63-334	.665-.738	.246-.334	0-.008	0-.018	0	Papiha <i>et al.</i> , 1982
Afghanistan	118-298	.696-.767	.157-.268	0	.023-.076	0	Benkmann <i>et al.</i> , 1980
Saudi Arabia	246	.474	.447	.020	.059	0	Goedde <i>et al.</i> , 1979a
South Africa (Negroid)	944	.282	.655	.034	.025	.004	Mauff <i>et al.</i> , 1976
Cameroon	275	.373	.595	.029	.003	0	Goedde <i>et al.</i> , 1979b
Tunisia	375	.617	.281	.019	.083	0	Davrinche <i>et al.</i> , 1981
Portugal	456	.654	.278	.043	.026	0	Weissmann and Reuter, 1981
Spain	330	.658	.266	.052	.022	0	Rodriguez-Córdoba <i>et al.</i> , 1981
France (Basque)	201	.550	.296	.139	.015	0	Ohayon <i>et al.</i> , 1980
Italy	161-431	.705-.768	.205-.236	.014-.022	.013-.037	0	Scherz <i>et al.</i> , 1982
Swiss	654	.805	.176	.010	.009	0	Scherz <i>et al.</i> , 1977
West Germany	1,245	.808	.174	.008	.009	.001	Mauff <i>et al.</i> , 1975
Norway	300	.817	.172	.005	.007	0	Teisberg and Olaisen, 1977
Norway (Lapp)	197	.888	.112	0	0	0	Teisberg and Olaisen, 1977

These racial differences in BF allele frequencies ensure that BF is a useful marker in the field of population genetics.

The C2 phenotypes observed in the present study are demonstrated in Fig. 1.

Fig. 1. Photograph of hemolytic overlay after isoelectric focusing showing four C2 phenotypes observed in Korean. 1 and 5, C; 2, BHC; 3, BC; 4, ATC.

Table 3. Distribution of C2 phenotype and allele frequencies in Korean.

Phenotype	Obs. No.	(%)	Exp. No.	Allele frequency
C	203	(92.3)	203.3	$C2^*C: 0.961 \pm 0.009$
BC	8	(3.6)	7.7	$C2^*B: 0.018 \pm 0.006$
BHC	5	(2.3)	4.8	$C2^*BH: 0.011 \pm 0.005$
ATC	4	(1.8)	3.8	$C2^*AT: 0.009 \pm 0.005$
Others	0	(0.0)	0.3	
Total	220	(100.0)	219.9	0.999

Table 4. Distribution of C2 allele frequencies in various populations.

Population	No.	C2 allele				Authors
		C	B	Others		
Korea	220	.961	.018	BH: .011	AT: .009	Present study
Japan	521	.939	.022	BH: .006	AT: .034	Tokunaga <i>et al.</i> , 1981
Thailand	184	.951	.049	0		Greiner <i>et al.</i> , 1980
Europe	274	.962	.038	0		Meo <i>et al.</i> , 1977
Norway	122	.97	.03	0		Olaisen <i>et al.</i> , 1978
West Germany	289	.965	.035	0		Dewald and Rittner, 1979

Table 5. Relationship between BF and C2 phenotypes.

		BF			Total
		F	FS	S	
C2	ATC	2	2	0	4
	BHC	1	3	1	5
	BC	0	3	5	8
	C	12	61	130	203
Total		15	69	136	220

Between C2 AT positive and BF F positive: $p=0.020$.

In addition to the common phenotype, C, three heterozygous phenotypes were observed. These were identified as BC, BHC, and ATC, respectively, by direct comparison with reference samples. The results of C2 typing of 220 unrelated healthy Koreans are presented in Table 3. The allele frequencies estimated for $C2^*C$, $C2^*B$, $C2^*BH$, and $C2^*AT$ were 0.961, 0.018, 0.011, and 0.009, respectively. The observed numbers of phenotypes were in good agreement with those expected under Hardy-Weinberg equilibrium.

Table 4 shows C2 allele frequencies in various populations. The frequencies of $C2^*C$ ($=C2^*1$) and $C2^*B$ ($=C2^*2$) in Korean are similar to those reported in other populations. However, two other variants observed in the present study, $C2^*BH$ (formerly A' , see Tokunaga and Omoto, 1982b) and $C2^*AT$, have been found in no other populations except in Japanese (Tokunaga *et al.*, 1981). This finding suggests the gene flow from Korea to Japan in the past.

Tokunaga *et al.* (1982a) reported the significant association of $C2^*AT$ with BF^*F and of $C2^*BH$ with BF^*F . Interestingly, the association between $C2^*AT$ and BF^*F was also found in the present study (Table 5, $p=0.020$ by Fischer's exact test).

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