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ORIGINAL INVESTIGATION

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Extensive polymorphism of ABO blood group gene: three major lineages of the alleles for the common ABO phenotypes

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Abstract Polymorphism of the ABO blood group gene was investigated in 262 healthy Japanese donors by a polymerase chain reactions-single-strand conformation polymorphism (PCR-SSCP) method, and 13 different alleles were identified. The number of alleles identified in each group was 4 for A^1 (provisionally called ABO*A101, *A102, *A103 and *A104 according to the guidelines for human gene nomenclature), 3 for B (ABO*B101, *B102 and *B103), and 6 for O (ABO*O101, *O102, *O103, *O201, *O202 and *O203). Nucleotide sequences of the amplified fragments with different SSCP patterns were determined by direct sequencing. Phylogenetic network analysis revealed that these alleles could be classified into three major lineages, *A/*O1, *B and *O2. In Japanese, *A102 and *B101 were the predominant alleles with frequencies of 83% and 97% in each group, respectively, whereas in group O, two common alleles, *O101 (43%) and *O201 (53%), were observed. These results may be useful for the establishment of ABO genotyping, and these newly described ABO alleles would be advantageous indicators for population studies.

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Introduction

The gene that determines ABO blood group, and which encodes a specific glycosyltransferase, was recently cloned and sequenced by Yamamoto et al. (1990a,b). As a result of these observations, several investigators have developed ABO genotyping methods that use polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis (Lee and Chang 1992; O'Keefe and Dobrovic 1993; Stroncek et al. 1995) and allele-specific PCR (Ugozzoli and Wallace 1992). Fischer et al. (1992) applied the PCR-RFLP method to the diagnosis of the acquired B status. Subsequently, Yamamoto et al. (1992, 1993a–d) determined the sequences of alleles for weak antigen groups, such as A^2, A^3, B^3, cis-AB, A^x and $B^{(A)}$, as well as another type of O allele.

From these observations, it seems that the polymorphism in the ABO blood group gene remains to be investigated. We have therefore developed a PCR-single-strand conformation polymorphism (SSCP) method for analyzing the extensive polymorphism of the ABO blood group gene.

Materials and methods

DNA samples

Genomic DNAs were prepared from peripheral blood leukocytes of 262 unrelated Japanese voluntary donors by standard phenol-chloroform extraction (Sambrook et al. 1989). The donors were composed of 74 blood group A_1, 73 group B, 61 group A_1B and 54 group O individuals.

Analysis by PCR-SSCP

PCR conditions and sequences of all primers are shown in Tables 1 and 2. PCR amplifications of four fragments (I–IV) performed with 35 amplification cycles in 10 μl of PCR reaction mixture (Bannai et al. 1994a). As shown in Fig. 1, PCR fragments I–IV cover the last two exons (exons 6 and 7) (Bennett et al. 1995; Yamamoto et al. 1995) of the ABO gene at nucleotide positions 240–374, 375–564, 526–855 and 845–1065, respectively. Total

Table 1 Nucleotide sequences of primers used in this study

Name	Sequence
Sense primers	
ABO-1	5′-CATGTGACCGCACGCCT-3′
ABO-3	5′-CCGTCCGCCTGCCTTGCAG-3′
ABO-5	5′-CAGCTGTCAGTGCTGGAGGTG-3′
ABO-7	5′-AAGAGGTGCAGCGGCTCACCA-3′
ABO-9	5′-GCCAAAGGTGCTGACACCG-3′
GS-AB	5′-AGGAAGGATGTCCTCGTGGTGG-3′
GS-O	5′-AGGAAGGATGTCCTCGTGGTA-3′
GS-AO	5′-CCATTGTCTGGGAGGGCATA-3′
Antisense primers	
ABO-2	5′-TCGGCCACCTCACTGACTTA-3′
ABO-4	5′-AAGTCACTGATCATCTCCAT-3′
ABO-6[a]	5′-CCGTTGGCCTGGTCGACCATCATGGCCTG-3′
ABO-8	5′-AGCCCTCCCAGAGCCCCTGGCA-3′
ABO-10	5′-TGCTAAAACCAAGGGCGGGA-3′

[a] Identical to FY-2 reported by Yamamoto et al. (1990a)

length of exons 6 and 7 is 826 bp (78% of the coding sequences) whereas that of exons 1–5 is 239 bp (22%).

SSCP analysis was performed essentially as described previously (Bannai et al. 1994a), using a 12.5%–15% polyacrylamide gel with or without 5% (by vol.) glycerol. Briefly, 1 μl of amplified DNA solution was mixed with 7 μl of denaturing solution, heated at 95°C for 5 min, and immediately chilled on ice; 1 μl of the mixture was subjected to polyacrylamide gel electrophoresis. The separated single-stranded DNA fragments in the gel were visualized by silver staining.

Group-specific PCR

As shown in Table 2, three sets of primers were used for group-specific PCRs: GS-AB and ABO-10 for groups A and B, GS-O and ABO-10 for group O, and GS-AO and ABO-10 for a part of the A and O alleles. These sense primers (GS-AB, GS-O and GS-AO) are located within fragment I, and the 3′-terminal of the antisense primer (ABO-10) is located 19 bases from the 3′-terminal of fragment IV (Fig. 1). Thus, these amplified fragments include fragments II through IV completely. The group-specific PCRs were performed under the same conditions as PCR-SSCP except that 5% (by vol.) dimethyl sulfoxide (DMSO) was added to the PCR mixture.

Table 2 Polymerase chain reaction (PCR) and single-stand confirmation polymorphism (SSCP) conditions for each primer pair

Sense primer	Antisense primer	Product length (bps)	PCR annealing temperature (°C)	SSCP		Remarks
				Gel concentration (%)	Electrophoretic temperature (°C)	
ABO-1	ABO- 2	187	60	15	12	Fragment I
ABO-3	ABO- 4	228	58	13	30	Fragment II
ABO-5	ABO- 6	380	66	13	26	Fragment III
ABO-7	ABO- 8	269	65	12.5*	30	Fragment IV
GS-AB	ABO-10	1900	61	–	–	Group-specific PCR
GS-O	ABO-10	1900	63	–	–	Group-specific PCR
GS-AO	ABO-10	1900	61	–	–	Group-specific PCR
ABO-3	ABO- 8	737	65	–	–	Template for direct
ABO-9	ABO-10	2500	63	–	–	sequencing

* With 5% glycerol

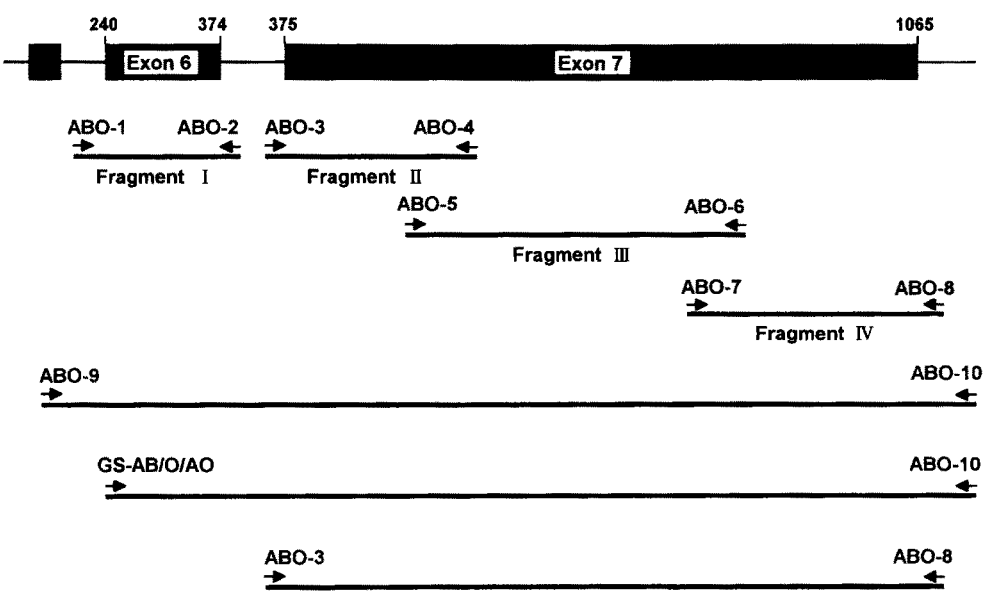

Fig. 1 Positions of primers and amplified fragments in the ABO gene. *Numbers* indicate the nucleotide positions of the 5′- and 3′-terminals of the last two exons

Direct sequencing

DNA templates for cycle-sequencing were produced by the following PCRs. For samples possessing only a single allele, fragments (approximately 2.5 kb including fragments I through IV and two introns) were amplified using the generic primer pair ABO-9 and ABO-10. For samples possessing two different alleles, a 737-bp fragment (fragments II through IV) was amplified by the primer pair ABO-3 and ABO-8 using the group-specific PCR products as templates. These amplified DNAs were purified as described previously (Bannai et al. 1994b) using a 1% low-melting-temperature agarose gel (BRL, Gaithersburg, Md., USA). The purified DNAs were then directly sequenced at least twice for each direction by a cycle-sequencing method with the same primers as used for PCR-SSCP, using an automated DNA sequencer (373A; Applied Biosystems, Foster City, Calif., USA).

Provisional classification of ABO alleles

The observed alleles were provisionally named according to the guidelines for human gene nomenclature (Shows et al. 1987).

Phylogenetic analysis

The maximum parsimony method (Fitch 1977) and the phylogenetic network method (Bandelt 1994) were used for delineating the relationship of alleles. The phylogenetic network method is closely related to the maximum parsimony method, although it may produce networks instead of trees. This method can be considered to be a generalization of a discordancy diagram (Fitch 1977). The computer program PAUP 3.1.1 (Univ. Illinois National History Survey) was used in the parsimony analysis, while the phylogenetic network was produced manually.

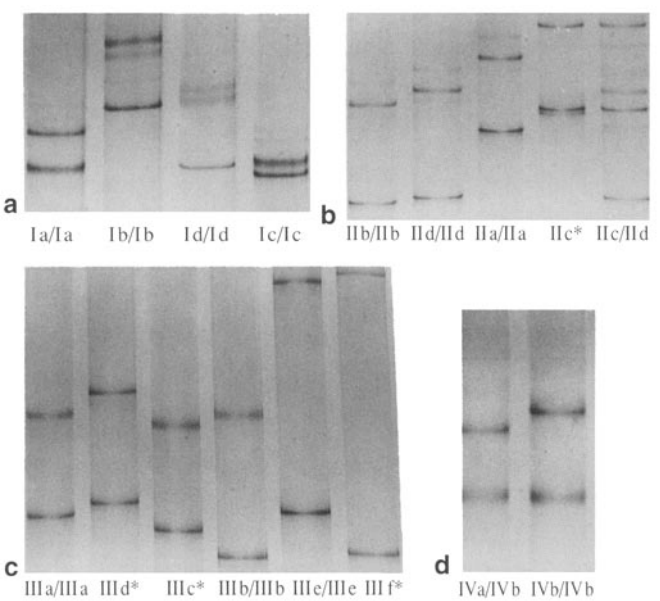

Fig. 2a–d PCR-SSCP analysis of the gene determining the ABO blood group. **a** Fragment I, four different homozygous samples; **b** fragment II, three different homozygous samples and one single allele (IIc*) obtained by group-specific PCR from a heterozygous sample (IIc/IId); **c** fragment III, three different homozygous samples and three different single alleles (IIIc*, IIId*, and IIIf*) obtained by group-specific PCRs; **d** fragment IV, two different homozygous samples

Table 3 SSCP patterns for each allele

Allele	SSCP pattern			
	F I	F II	F III	F IV
ABO*A101	Ia	IIa	IIIa	IVa
*A102	Ia	IIb	IIIa	IVa
*A103	Ia	IIc	IIIa	IVa
*A104	Ib	IIa	IIIa	IVa
ABO*B101	Ib	IId	IIIb	IVb
*B102	Ib	IId	IIIb	IVa
*B103	Ib	IId	IIIc	IVb
ABO*O101	Ic	IIa	IIIa	IVa
*O102	Ic	IIa	IIId	IVa
*O103	Id	IIa	IIIa	IVa
*O201	Id	IIa	IIIe	IVa
*O202	Ic	IIa	IIIe	IVa
*O203	Id	IIa	IIIf	IVa

Results

ABO alleles identified by PCR-SSCP

Genomic DNAs from 262 donors with known ABO phenotypes, which were determined by serology, were examined by PCR-SSCP. A typical SSCP pattern obtained from a sample of an individual possessing a single allele showed two bands, corresponding to sense and antisense strands, and the fragments derived from two different alleles showed four bands (Fig. 2). In a few cases, three-band patterns were observed, although the samples carried single alleles (Fig. 2a). This was probably due to electrophoresis of a large amount of DNA, or to equilibration of two different conformations of single-stranded DNA fragments. The numbers of different SSCP patterns observed for each fragment were four for fragment I, four for fragment II, six for fragment III, and two for fragment IV. The alleles were identified based on the combination of the SSCP patterns of these four fragments. When SSCP patterns of fragments I–IV showed only a single pattern with two bands, the sample was judged to be from a homozygote carrying a common allele. Forty-four out of the 262 samples were judged to be homozygotes for common alleles and 195 samples as heterozygotes possessing these common alleles.

Uncommon alleles were identified by subtracting the patterns of the common alleles from those observed in the remaining 23 heterozygous samples. These rare alleles were further analyzed to confirm the combination of fragments I–IV using nested PCR. By group-specific PCRs, only one allele out of the two in heterozygotes could be specifically amplified (first PCR); with the primer pair GS-AB/ABO-10 for groups A and B, GS-O/ABO-10 for group O, and GS-AO/ABO-10 for a part of the A and O alleles. The DNA fragments obtained from the single allele including fragments II–IV were then subjected to PCR-SSCP analysis for each fragment (second PCR). Thus, the SSCP patterns of these fragments showed only two bands as demonstrated in Fig. 2b, c.

As shown in Table 3, the SSCP patterns observed in group A^1 were provisionally called Ia and Ib for fragment I, IIa, IIb and IIc for fragment II, IIIa for fragment III, and IVa for fragment IV. Consequently in group A^1, we identified four different alleles, ABO*A101, *A102, *A103 and *A104, based on the combination of SSCP patterns. Among them, ABO*A101 and *A102 were observed in the homozygous state.

In group B, the observed SSCP patterns were Ib for fragment I, IId for fragment II, IIIb and IIIc for fragment III, and IVb for fragment IV. Among them, IId, IIIb and IIIc were exclusively observed in group B. Consequently in group B, we identified three different alleles, with ABO*B101 being the predominant one.

In group O, the observed SSCP patterns were Ic and Id for fragment I, IIa for fragment II, IIIa, IIId, IIIe and IIIf for fragment III, and IVa for fragment IV. Among them, Ic and Id were restricted to group O. Two of the six O alleles, ABO*O101 and *O201, were commonly observed.

In total, we identified 13 different alleles. Moreover, PCR-SSCP analysis of fragments I and II, or fragments I and III, allowed us to determine the common ABO genotypes: SSCP patterns Ic or Id for O, IId and IIIb or IIIc for B, and other patterns of fragments I–III for A^1.

Nucleotide sequences of ABO alleles

All of the DNA fragments that were distinguished from each other by SSCP analysis were sequenced in order to reveal any identity with previously reported sequences. Figure 3 shows a summarized schema of the sequencing results.

In group A^1, ABO*A101 had an identical sequence to that of the cDNA clone FY-66-1 described by Yamamoto et al. (1990b). ABO*A102 had a single nucleotide substitution at codon 156 as compared with ABO*A101: ABO*A102 has CTG coding for leucine, while ABO*A101 has CCG coding for proline. The same substitution had already been observed in FY-59-5 (Yamamoto et al. 1990a), but the sequence of this clone differed by a three-base deletion at nucleotide positions 240–242 from that of the other clones (Yamamoto et al. 1990b) and the present alleles including ABO*A102. [Concerning the nucleotide numbering system in the ABO gene, the previous numbers (Yamamoto et al. 1990a, b) are different from the more recent numbers (Yamamoto et al. 1992, 1993a–d) used in this study.] ABO*A103 had a single synonymous substitution at nucleotide position 564 as compared with ABO*A102. ABO*A104 and *A101 differed by a single synonymous substitution at position 297 (G and A, respectively).

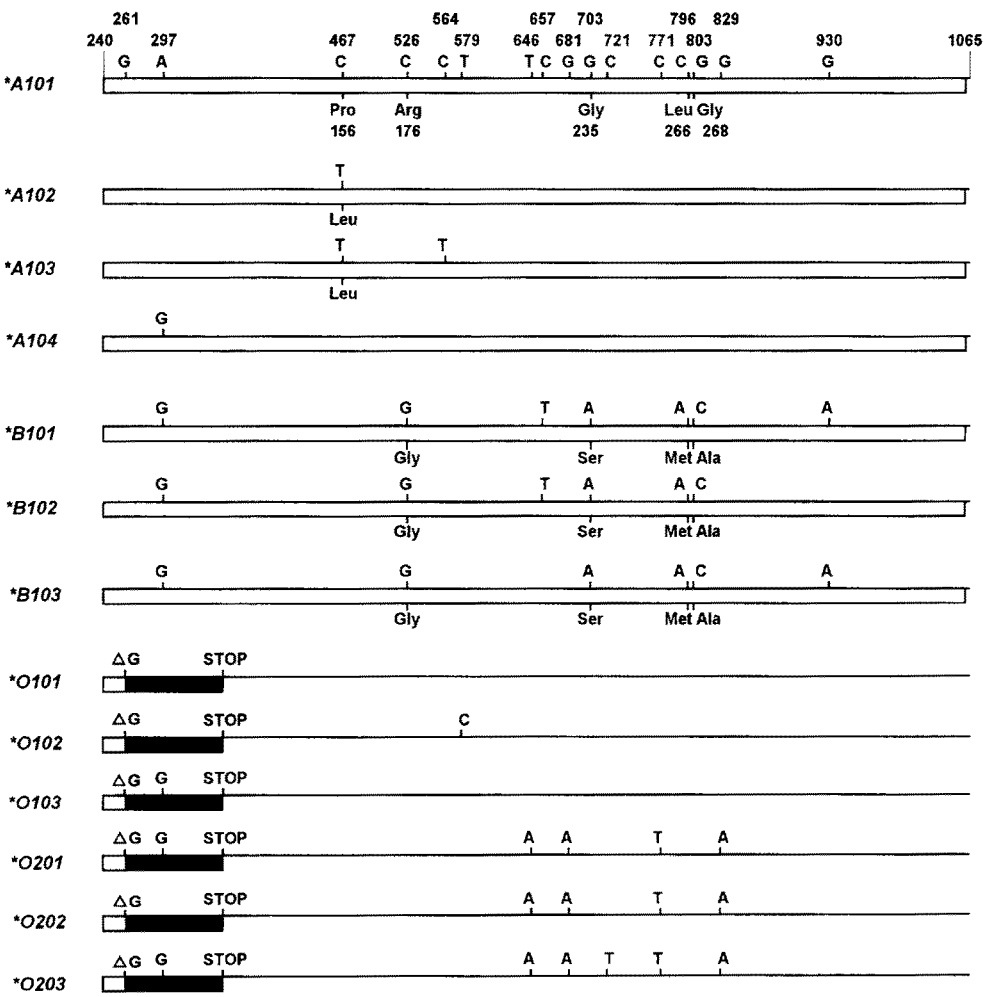

Fig. 3 Schematic comparison of nucleotide and deduced amino acid sequences of the ABO alleles identified by PCR-SSCP. Only the differences from the nucleotide and amino acid sequences of *A101 are indicated. An entirely different amino acid sequence in O alleles (■) resulting from frame-shifting caused by a single base deletion. *A101, *B101, *O101 and *O201 have sequences identical to previously described ABO alleles (Yamamoto et al. 1990a,b)

In group B, ABO*B101 had an identical sequence to that of a previously described B allele (Yamamoto et al. 1990b), whereas ABO*B102 and *B103 had synonymous substitutions that differed from *B101 at positions 930 (A to G) and 657 (T to C), respectively.

In group O, all six alleles shared a single nucleotide deletion (G) at position 261, resulting in a shift in the reading frame that leads to the appearance of a stop codon at positions 353–355. These six alleles could be classified, according to the substitutions and phylogenetic network described below, into two subgroups, ABO*O1 and *O2. ABO*O101 was different from ABO*O201 by five nucleotide substitutions at positions 297, 646, 681, 771, and 829, and both alleles were identical to the previously described O alleles (Yamamoto et al. 1990b, 1993c). ABO*O102 and *O103 had a one-nucleotide substitution compared with ABO*O101 at positions 579 (T to C) and 297 (A to G), respectively. Similarly, ABO*O202 and *O203 had a one-nucleotide substitution compared with ABO*O201 at positions 297 (G to A) and 721 (C to T), respectively.

Thus, 9 of the 13 alleles (ABO*A102, *A103, *A104, *B102, *B103, *O102, *O103, *O202 and *O203) were newly sequenced ABO alleles, but none of their nucleotide substitutions, except for position 467 of *A102 and *A103, lead to amino acid changes.

Estimation of allelic frequencies

We selected samples from a total of 262 healthy Japanese donors, in which 74 A_1, 73 B, 61 A_1B and 54 O phenotypes were included, and ABO allele frequencies in each group were examined by PCR-SSCP analysis (Table 4). Within group A^1, ABO*A102 was most common at a frequency of 83%. Although ABO*A101 had an identical sequence to that of the A^1 allele described by Yamamoto et al. (1992), its estimated frequency in the Japanese population was much lower than that of ABO*A102 (approximately one-fifth). Within group B, ABO*B101 was the predominant allele at a frequency of 97%. In contrast, within group O, both ABO*O101 and *O201 were common with similar frequencies (43% and 53%, respectively).

Table 4 Allele frequencies in ABO system

Allele	n	Proportion within each group
ABO*A101	23	15.4
*A102	123	82.6
*A103	1	0.7
*A104	2	1.3
Total	149	100.0
ABO*B101	138	97.2
*B102	3	2.1
*B103	1	0.7
Total	142	100.0
ABO*O101	100	42.9
*O102	3	1.3
*O103	1	0.4
ABO*O201	123	52.9
*O202	5	2.1
*O203	1	0.4
Total	233	100.0

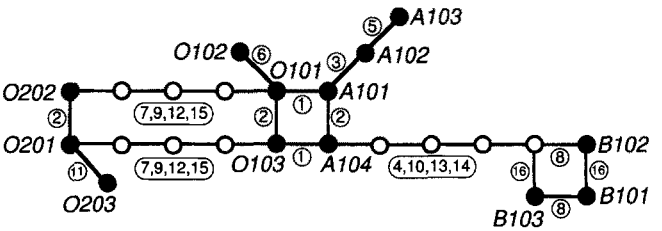

Fig. 4 A phylogenetic network for the 13 ABO alleles (denoted by *full circles*). *Open circles* indicate intermediate states. *Numbers in circles* correspond to the following polymorphic sites: 1 = 261, 2 = 297, 3 = 467, 4 = 526, 5 = 564, 6 = 579, 7 = 646, 8 = 657, 9 = 681, 10 = 703, 11 = 721, 12 = 771, 13 = 796, 14 = 803, 15 = 829, 16 = 930

Phylogenetic tree of ABO alleles

We first applied the maximum parsimony method to the sequence data of the 13 ABO alleles for reconstructing the phylogenetic tree. Thirty-six equally parsimonious trees were produced using PAUP 3.1.1 with the branch-and-bound option. When interior branches with length zero were ignored, however, the number of distinct tree topologies was reduced to 16 (trees not shown). Clearly, the maximum parsimony method is not appropriate for delineating the complex nature of the polymorphism of the ABO alleles.

We also used the phylogenetic network method, and the resulting single network is presented in Fig. 4. There are three rectangles in that network, indicating the existence of mutually incompatible sites. For example, the rectangle consisting of three B alleles is produced because the nucleotide configuration for site 8 (position 657 in Fig. 3) is inconsistent with that for site 16 (position 930 in Fig. 3). Either site is assumed to experience parallel substitutions. In any case, all the 16 equally parsimonious trees can be created from this single network.

Discussion

Since the molecular structure of the gene determining the ABO blood group has recently been elucidated (Yamamoto et al. 1990a,b), several DNA typing methods including PCR-RFLP analysis and allele-specific PCR have been described. These methods might be applicable in forensic science (Lee and Chang 1992; Matsuki et al. 1994; Fukumori et al. 1995), laboratory diagnosis (Fischer et al. 1992) and population studies (Grunnet et al. 1994; Franco et al. 1994) with limited ABO alleles as the sub-

jects. Although PCR-RFLP and allele-specific PCR methods are useful for detecting variations in the recognition sequences of certain restriction enzymes or specific primers, they cannot necessarily be used to detect alleles with unknown substitutions in the amplified DNA fragments. Recently, Johnson and Hopkinson (1992) described four different O alleles, as well as two B and one A allele from unrelated European individuals by means of denaturing gradient gel electrophoresis, but no sequence analysis was performed. From their observations and a personal communication (K. Kobayashi), the number of different alleles in the ABO blood group system is considered to be much more than generally anticipated.

In this study, we applied a PCR-SSCP method to detect different ABO alleles. This method enabled us to detect point mutations at various positions (Orita et al. 1989) in the amplified fragments, and it can be used to determine the ABO genotypes as well as to detect undescribed ABO alleles. In this PCR-SSCP analysis, we identified 13 different alleles and the numbers of alleles in groups A^1, B and O were 4, 3 and 6, respectively. Four of them, ABO*A101, *B101, *O101 and *O201, had sequences identical to those of the previously described ABO alleles (Yamamoto et al. 1990a, b). The other nine alleles, ABO*A102, *A103, *A104, *B102, *B103, *O102, *O103, *O202 and *O203 were newly observed.

ABO*A102 has an identical sequence to that of ABO*A101 except for a single base substitution at nucleotide position 467 (C to T). ABO*A103 and *A104 have only one or two nucleotide substitutions compared with ABO*A101 or *A102, and thus these 4 ABO*A alleles may belong to a single evolutionary lineage.

Yamamoto et al. (1990b) described a B allele with seven nucleotide substitutions compared with an A^1 allele, and four of them lead to amino acid changes that may be responsible for the specificity of A_1 or B transferase. These four nucleotide substitutions were also observed in the three B alleles observed in the present study. ABO*B102 and *B103 have only one nucleotide substitution compared with ABO*B101. Thus, these three ABO*B alleles belong to a single evolutionary lineage, which is different from the ABO*A lineage.

In group O, we identified six different alleles, all of which shared a single nucleotide deletion at position 261. In contrast, in the Japanese population samples examined to date, we could not find another type of O allele named O^2 (Yamamoto et al. 1993d; Franco et al. 1994). ABO*O101 has an identical sequence to that of ABO*A101 except for a single nucleotide deletion. ABO*O102 and *O103 have one nucleotide substitution compared with ABO*O101. Thus, these three alleles may belong to the same evolutionary lineage as ABO*A. In contrast, ABO*O201 has 5 nucleotide substitutions compared with ABO*O101. Moreover, ABO*O202 and *O203 have one nucleotide substitution relative to ABO*O201, and thus these three alleles may belong to another lineage, which is different from the *A or *B lineage.

These results indicate that the Japanese ABO alleles are divided into three major lineages, *A/*O1, *B and *O2. Phylogenetic network analysis of these ABO alleles supported the above hypothesis.

Our PCR-SSCP method may be useful for the elucidation of the variety of the ABO gene as well as the establishment of ABO genotyping. Furthermore, the method would be applicable for identifying alleles that determine uncommon phenotypes.

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