

REVIEW

Biological and clinical aspects of ABO blood group system

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Abstract : The ABO blood group was discovered in 1900 by Austrian scientist, Karl Landsteiner. At present, the International Society of Blood Transfusion (ISBT) approves as 29 human blood group systems. The ABO blood group system consists of four antigens (A, B, O and AB). These antigens are known as oligosaccharide antigens, and widely expressed on the membranes of red cell and tissue cells as well as, in the saliva and body fluid.

The ABO blood group antigens are one of the most important issues in transfusion medicine to evaluate the adaptability of donor blood cells with bone marrow transplantations, and lifespan of the hemocytes.

This article reviews the serology, biochemistry and genetic characteristics, and clinical application of ABO antigens. *J. Med. Invest.* 55 : 174-182, August, 2008

Keywords : ABO blood group, glycosyltransferase, ABO allele, cisAB allele, PASA : PCR amplification of specific alleles

INTRODUCTION

The ABO blood group system was discovered by Austrian scientist, Karl Landsteiner, who found three different blood types (A, B and O) in 1900 from serological differences in blood called the Landsteiner Law (1). In 1902, DesCasterllo and Sturli discovered the fourth type, AB (2). The ABO blood group is most important among the 29 blood group systems (Table 1), and consists of four antigens (A, B, O and AB) (3, 4). In 1924, Felix Bernstein predicted by extensive family studies that the mechanism of inheritance involved in three alleles at the ABO locus (5). Furthermore, the structure and biochemical characteristics of the ABO antigens were elucidated by many investigators.

The genes of ABO blood group has been determined at chromosome locus 9 (6-9), and Yamamoto, *et al.* cloned and determined the structures. It has made it possible to analyze genetically ABO blood group antigens using molecular biology techniques (7, 10-18).

SEROLOGY OF ABO BLOOD GROUP SYSTEM

The ABO blood group is determined by the presence of A and B antigens on the surface of the red blood cells, and of anti-A or anti-B antibodies in the serum. Thus, the red blood cells of blood type A possess antigen A and the serum containing anti-B antibody. Similarly, blood type B has antigen B and anti-A antibody. Blood type AB contains both A and B antigens but no antibodies. Blood type O has no antigens but contains both anti-A and anti-B antibodies. Anti-A and anti-B antibodies are usually IgM type, and not present in newborns, but

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Table 1 ISBT Human Blood Group Systems

ISBT No.	System name	ISBT symbol	Locus	ISBT No.	System name	ISBT symbol	Locus	ISBT No.	System name	ISBT symbol	Locus
001	ABO	ABO	9	011	Yt	YT	7	021	Cromer	CROM	1
002	MNS	MNS	4	012	Xg	XG	X	022	Knops	KN	1
003	P	P1	22	013	Scianna	SC	1	023	Indian	IN	11
004	Rh	RH	1	014	Dombrock	DO	12	024	Ok	OK	19
005	Lutheran	LU	19	015	Colton	CO	7	025	Raph	RAPH	11
006	Kell	KEL	7	016	Landsteiner-Wiener	LW	19	026	John Milton Hagen	JMH	15
007	Lewis	LE	19	017	Chido/Rodgers	CH/RG	6	027	I	I	6
008	Duffy	FY	1	018	H	H	19	028	Globoside	GLOB	3
009	Kidd	JK	18	019	Kx	XK	X	029	Gill	GIL	9
010	Diego	DI	17	020	Gerbich	GE	2				

appear in the first year of life. It is possible that the antibodies are produced against food and environmental antigens (bacterial, viral or plant antigens) (19, 20), which are similar in structure to A and B antigens. This is summarized in Table 2 (21).

BIOCHEMISTRY

1) ABO blood group

A) Model of antigen carrier proteins

Blood group antigens are surface markers on the

red cell, and consist of proteins and carbohydrates attached to lipids or proteins. A model of the membrane components carrying blood group antigens is shown in Figure 1 (22).

B) The structure and biosynthesis of ABO antigens

ABO antigens are one of the oligosaccharides antigens (23). These antigens are widely expressed on the membranes of red cell and tissue cell as well as, in the saliva and body fluid (24).

As shown in Figure 2, the first step in the biosynthesis of ABO antigens is the addition of a L-fucose in $\alpha 1 \rightarrow 2$ linkage on terminal galactose (Gal)

Table 2 Frequency of Japanese ABO blood groups

Phenotype	Blood group			Red Blood Cell Surface Antigens	Serum Antibodies
	Frequency (%)	Genotype	Frequency (%)		
A	39.8	A/A A/O	8 31	A	Anti-B
O	29.9	O/O	29	–	Anti-A, Anti-B
B	19.9	B/B B/O	3 19	B	Anti-A
AB	9.9	A/B	10	A, B	–

Model of Antigen Carrier Proteins

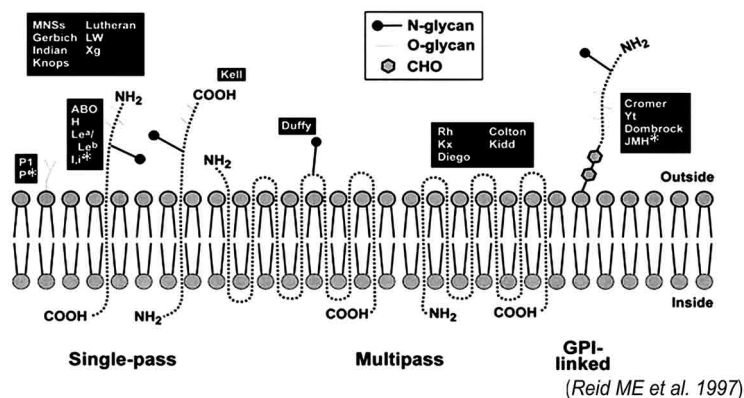
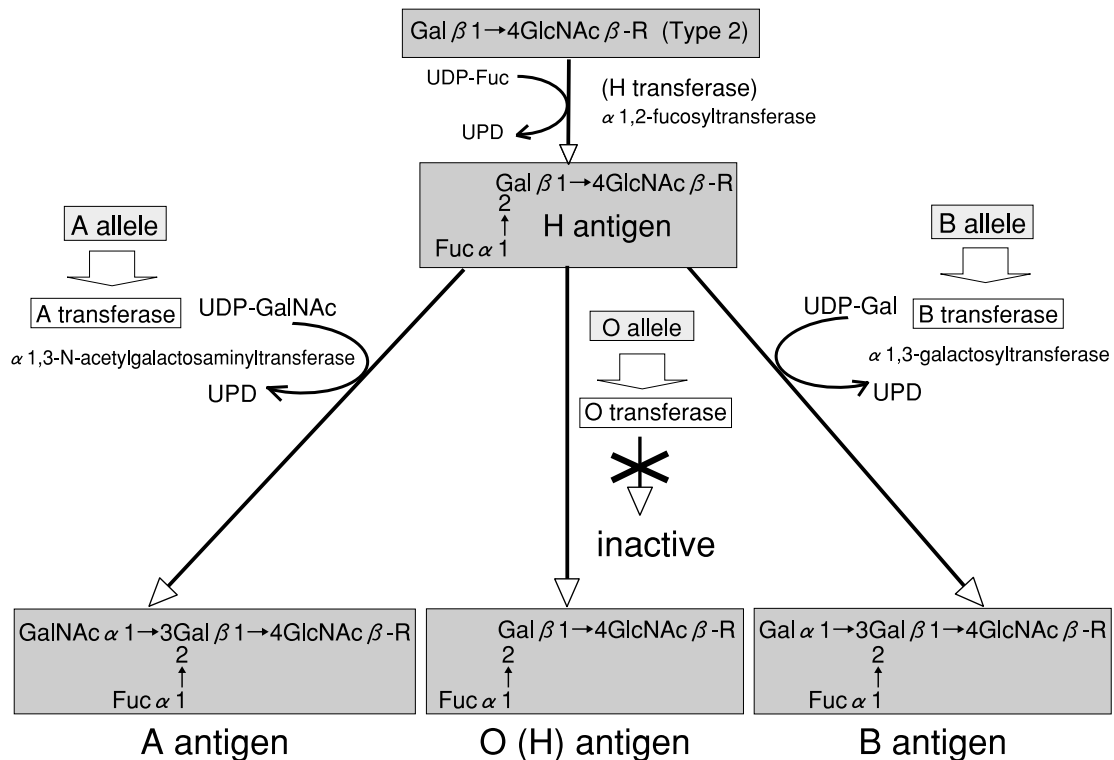


Figure 1. Model of RBC membrane components that carry blood group antigens.

* : Blood group collections or high incidence antigen. The Ch/Rg and Scianna blood group system are not shown in this figure.



Fuc : L-fucose, Gal : D-galactose, GalNAc : N-acetylgalactosamine, GlcNAc : N-acetylglucosamine

Figure 2. Biosynthesis of ABO antigens.

of a common precursor attached to lipids or proteins by $\alpha 1,2$ -fucosyltransferase (H transferase), resulting in the H antigen. Six different types of the common precursor structure are known (25); Type 1 (Gal $\beta 1 \rightarrow 3$ GlcNAc β -R) and Type 2 (Gal $\beta 1 \rightarrow 4$ GlcNAc β -R) sequences are the main structures. Type 1 is substance in secretions and tissues, and Type 2 is an antigen on the surface of the red blood cells. A, B and O (H) antigenic structures on the surface of red cells are defined as carbohydrate determinants, GalNAc $\alpha 1 \rightarrow$ (Fuc $\alpha 1 \rightarrow 2$)3Gal $\beta 1 \rightarrow 4$ GlcNAc β -R, Gal $\alpha 1 \rightarrow$ (Fuc $\alpha 1 \rightarrow 2$)3Gal $\beta 1 \rightarrow 4$ GlcNAc β -R, and (Fuc $\alpha 1 \rightarrow 2$)Gal $\beta 1 \rightarrow 4$ GlcNAc β -R, respectively, which are synthesized from the H antigen structure by the action of specific glycosyltransferase products of ABO genes. The A and B alleles encode glycosyltransferase ($\alpha 1,3$ -N-acetylgalactosaminyltransferase (A transferase) and $\alpha 1,3$ -galactosyltransferase (B transferase)), which catalyze the addition of specific sugars, N-acetylgalactosamine (GalNAc) and galactose (Gal) residue, respectively, in a $\alpha 1 \rightarrow 3$ linkage on terminal Gal of H antigen (6, 26-28). Since O allele encodes proteins without glycosyltransferase (O transferase) function, H antigen is the only ABO structure present in blood type O (29).

C) Structure of the ABO gene locus

Human ABO genes are located in chromosome 9q34.1-q34.2(6-9) and consists of 7 exons distributed over 18 kb of genomic DNA. Exon 7 contains most of the largest coding sequence. Exon 6 contains the deletion found in most O alleles. The exons range in size from 28 to 691 bp (29).

The ABO locus has three main allele forms, A, B, and O. A and B alleles have seven nucleotide substitutions (297A>G, 526C>G, 657C>T, 703G>A, 796C>A, 803G>C and 930G>A). Four nucleotide substitutions (526C>G, 703G>A, 796C>A and 803G>C) are translated into different amino acid substitutions (Arg526Gly, Gly703Ser, Leu796Met and Gly803Ala). These substitutions determine the specificities of glycosyltransferases. The A allele encodes A transferase catalyzing the addition of GalNAc residue, and the B allele encodes B transferase catalyzing the addition of Gal residue, respectively, in a $\alpha 1 \rightarrow 3$ linkage on terminal Gal of the H antigen. On the other hand, the O allele differs from the A allele by a single nucleotide deletion of guanine (G) at position 261. This deletion causes a frame-shift and results in a loss of transferases activity (Figure 3) (29-31).

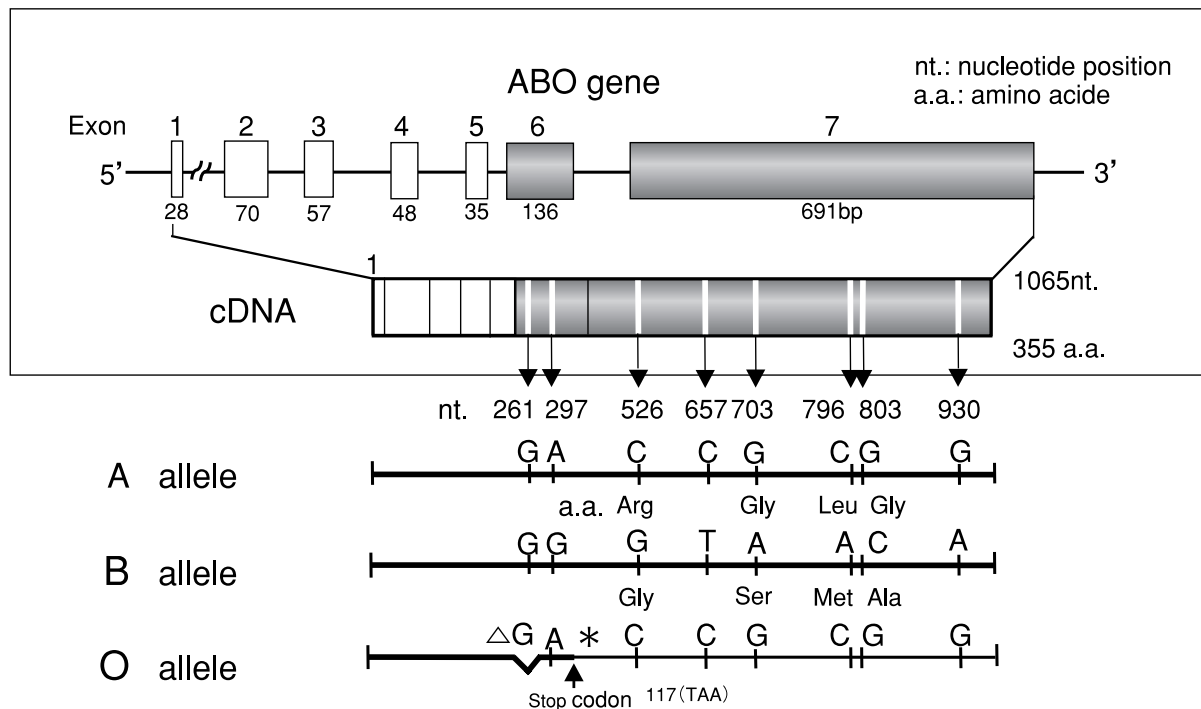


Figure 3. Structure of the ABO gene locus and nucleotide sequences of A, B and O alleles.

Diagram of exon organization of the protein coding sequences (upper shaded). * ; Entirely different deduced amino acid sequence in O alleles due to frame-shifting caused by a single base deletion (lower).

2) Subgroups

A) Subgroups of A and B

An ABO blood group subtype is called a subgroup and/or variant. Subgroups of ABO are distinguished by decreased amounts of A, B or O (H) antigens on red blood cells. The most common are subgroups of A and B.

Blood type A appears to have the most variation in subgroups. Blood type A with a normal quantity of antigen is called A_1 , and is distinguished from subgroups. Subgroups are classified by the quantity of A antigen, and the amount of A antigen decreases in the order A_1 , A_2 , A_3 , A_x , A_{end} , A_m , A_{el} . In Europeans, approximately 80% of blood type A and AB belong to A_1 , the remaining 20% are either A_2 or A_2B (in Japanese it is approximately 0.2%) (32, 33).

In general, serologic distinction between A_1 and A_2 is based on the agglutination of A_1 red blood cells but not A_2 cells with anti- A_1 lectin (extract of *Dolichos biflorus* seeds) (34). Recently, the sequence of A_2 allele coding blood type A_2 has been molecular genetically analyzed, and shown to have a single base deletion near the carboxyl terminal. The deletion causes a frame-shift and results in a loss of A_2 transferase activity. This deletion of A_2 allele made it possible to analyze genetically blood

type A_2 (35). Similarly, subtypes of blood type B are classified by the quantity of B antigen, and the amount of B antigen decreases in the order B, B_3 , B_x , B_m , B_{el} . The expression of A or B antigens is summarized in Table 3 (36, 37).

Table 3 Expression of ABO antigens per red blood cell surface

Blood group type		Expression
A_1	adult	810,000 ~ 1,170,000
A_1	newborn	250,000 ~ 370,000
A_2	adult	240,000 ~ 290,000
A_2	newborn	140,000
A_1B	adult	460,000 ~ 850,000
A_1B	newborn	240,000 ~ 290,000
A_2B	adult	120,000
A_3		7,000 ~ 100,000
A_x		1,400 ~ 10,000
A_{end}		1,100 ~ 4,400
A_m		200 ~ 1,900
A_{el}		100 ~ 1,400
B	adult	610,000 ~ 830,000
B	newborn	200,000 ~ 320,000
A_1B	adult	310,000 ~ 560,000

B) Subgroups of AB

Blood type AB is classified into nine subtypes (A_xB , A_1B_x , A_mB , A_1B_m , $A_{el}B$, A_1B_{el} , $cisA_2B_3$, $cisA_2B$, $cisA_1B_3$) by the quantity of A or B antigen. In particular, $cisAB$ is a very rare phenotype and has three blood types, $cisA_2B_3$ (A_2B_3/O), $cisA_2B$ (A_2B_3/B), $cisA_1B_3$ (A_2B_3/A_1). Detecting this AB variant is

very important, especially in blood transfusion and in dissolving a problem of paternity in the ABO blood group system.

In 1964, Seyfried, *et al.* reported a family consisting of a woman with AB, her husband with blood type O, and daughter with blood type AB. They described the strange inheritance of blood type A and B and suggested that these specificities might be coded by genes located on the same chromosome (38).

In 1966, Yamaguchi, *et al.* reported a family which consisted of three children with blood group A₂B₃ born to a father (blood type O) and mother (blood group A₂B₃). This family lived in Tokushima Prefecture in Japan. This finding showed that the A and B genes were located on the same chromosome. They proposed the name "CisAB" to distinguish it from ordinary AB, namely "Trans AB" (39). It has been reported that the frequency of this phenotype is apparently higher in Tokushima, Ishikawa and Kagawa Prefectures than in other prefectures in Japan. For example, the frequency of the cisAB phenotype in Tokushima Prefecture (0.017% - 0.02%) is about 11 times as high as that in

Osaka Prefecture (0.0014% - 0.0017%) (40, 41). Furthermore, it is interesting that some cisAB families in other prefectures had actually moved from Tokushima over the last several generations. These findings suggest that families with the cisAB blood phenotype might have common ancestors.

Recently, the nucleotide sequence of the coding region in the last two coding exons of ABO genes from cisAB individuals was determined. CisAB (A₂B₃) alleles were identical to one another while different from the A₁ allele by two nucleotide substitutions (Figure 4). Both of these nucleotide substitutions result in amino acid substitutions (42). The first substitution is identical to that previously found in the A₂ allele, corresponding to the cisAB (A₂B₃) allele encoding a glycosyltransferase that is capable of synthesizing both A and B antigens (17, 18, 35).

Therefore, the phenotype of the ABO blood group system, such as subgroups of A, B and AB, have been realized by changes in the cDNA sequence, for example, base substitution or deletion. Comparison of the nucleotide sequences of alleles in A, B and AB subgroups is summarized in the Table 4 (43-45).

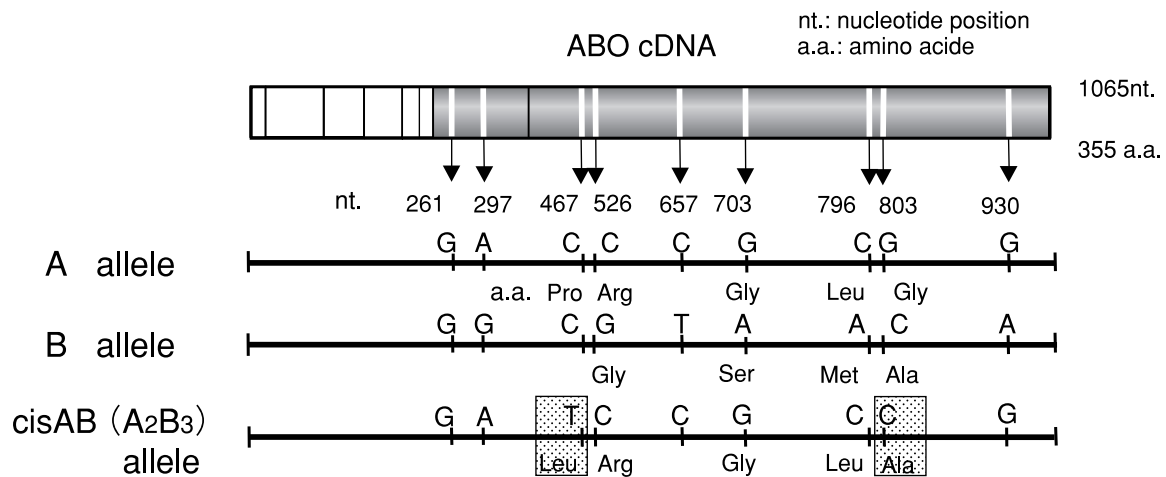


Figure 4. Structure of the ABO gene locus and nucleotide sequences of A, B and cisAB alleles. Diagram of exon organization of the protein coding sequences (upper shaded).

Table 4 Comparison of the nucleotide sequences of alleles in A, B and AB subgroups

	Entire coding sequence determined with cDNA														nt.
	261	297	467	526	646	657	703	796	802	803	871	930	1054	1059-1061	
A ₁ allele	G	A	C	C	T	C	G	C	G	G	G	G	C	C	
A ₂ allele			T											C-del	
A ₃ allele											A				
A _x allele					A										
B allele		G		G		T	A	A		C		A			
B ₃ allele		G		G		T	A	A		C		A	T		
cis AB allele			T							C					

(Vox Sang, 1995, Yamamoto *et al.*)

GENETIC ANALYSES OF ABO BLOOD GROUPS AND THEIR APPLICATIONS FOR CLINICAL STUDIES

Gene technology using PCR has markedly advanced in recent years and has been introduced into clinical laboratories. Accordingly, genotypes of the ABO blood group have been analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), PCR-direct sequencing, PCR-single strand conformation polymorphism (PCR-SSCP), and PCR-amplification of specific alleles (PASA). PCR-RFLP, PCR-direct sequencing and PCR-SSCP methods require 2-step procedures, and then not easy to be used in clinical laboratories. The PASA method is based on the fact that PCR amplification occurs only when the 3' endbase of the primer is matched to the nucleotide of No. 261, 526, 796 or 803 (the sites of amino acid substitutions) of ABO allelic cDNA, and three of five regions of allelic DNAs were co-amplified in single PCR (multiplex-PCR) in our study (8, 12-16). ABO and cisAB blood group genotypes were

directly determined, based on the molecular size of allele-specific amplification products. The PASA method requires only about 4 hours from the start of PCR to the end of analysis. Therefore, PASA method is rapid, simple and useful for detecting the genotype of ABO and cisAB blood groups in comparison with PCR-RFLP, PCR-direct sequencing and PCR-SSCP methods and used widely throughout the research and clinical laboratories.

The scheme of the method of amplification and the analysis of specific ABO and cisAB alleles using the PASA method are shown in Figure 5 (14).

1) ABO genotyping

As shown in Figure 6 (13), all genes of the six major ABO genotypes, *A/O*, *A/A*, *B/O*, *B/B*, *O/O* and *A/B* were amplified; three specific bands (379, 104 and 52bp) for *A/O*, two specific bands (379 and 52bp) for *A/A*, four specific bands (379, 224, 104 and 52 bp) for *B/O*, two specific bands (224 and 52bp) for *B/B*, two specific bands (379 and 104 bp) for *O/O* and three specific bands (379, 224 and 52bp) for *A/B*.

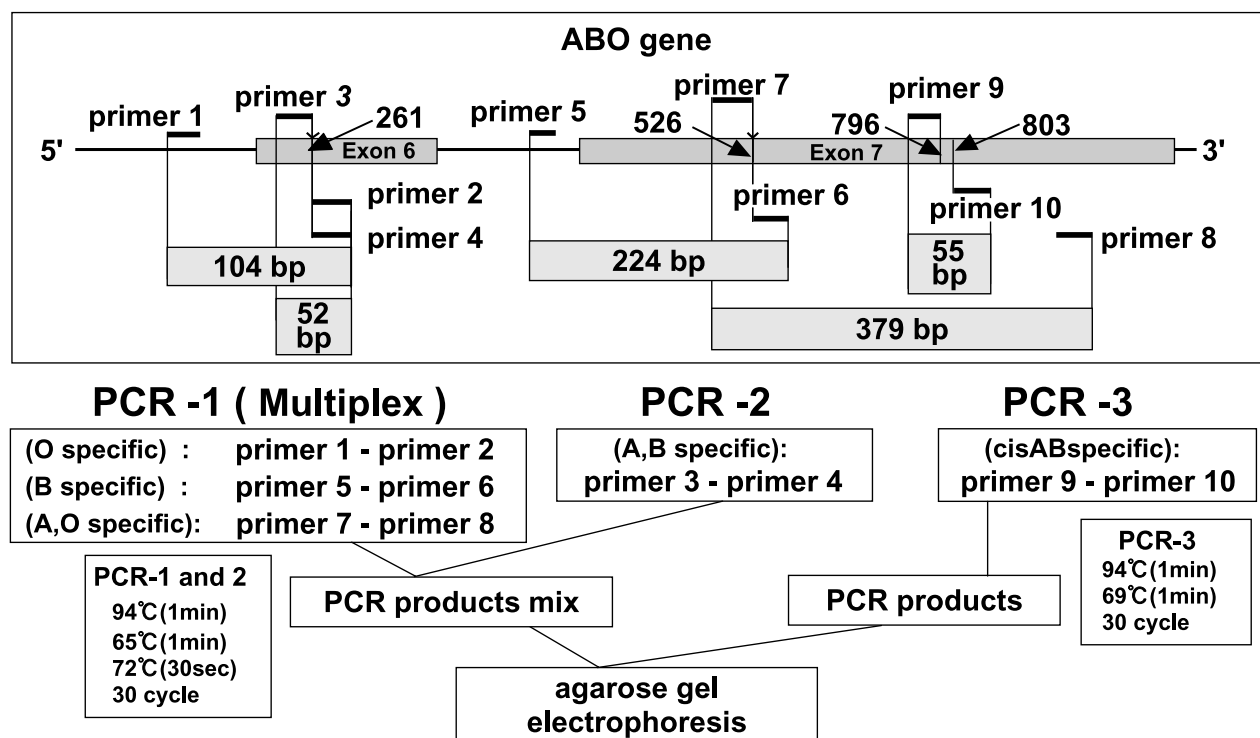


Figure 5. Scheme of method of amplification and analysis of specific ABO alleles using the PASA method.

3' endbase of primer 2, 3 and 4, 6, 7, 9 and 10 corresponded to the nucleotide sequences of O, A and B, B, A and O, and cisAB alleles, respectively. Primer 1, 5 and 8 corresponded to nucleotide sequences of the ABO allele. Allele-specific DNA fragments of O allele (104 bp), A and B allele (52 bp), B allele (224 bp), A and O allele (379 bp), and cisAB (55bp) were amplified by PCR with 5 pairs of primers (primer 1 and 2, primer 3 and 4, primer 5 and 6, primer 7 and 8, and primer 9 and 10), respectively. Three (104bp, 224bp and 379bp) of five fragments were co-amplified in a single PCR-1 (multiplex-PCR).

ABO specific

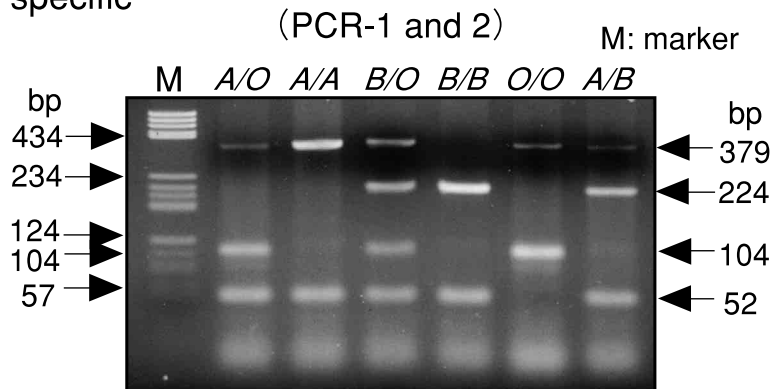


Figure 6. Electrophoretic patterns of PCR products in the six major ABO genotypes. Genomic DNA extracted from leukocytes was amplified by the PASA method using 4 primer sets (primer 1 and 2, primer 3 and 4, primer 5 and 6, and primer 7 and 8). M, Hae III digest of Plasmid pBR322 (marker).

2) *cisAB* genotyping

As shown in Figure 7 (13, 14), all genes of the three major *cisAB* genotypes, A_2B_3/O , A_2B_3/A_1 and A_2B_3/B were amplified; four specific bands (379, 104, 52 and 55 bp) for A_2B_3/O , three specific bands (379, 52 and 55 bp) for A_2B_3/A_1 and four specific bands (379, 224, 52 and 55 bp) for A_2B_3/B .

Table 5 summarizes all possible specific band patterns of the ABO genotype obtained with the PASA method. ABO and *cisAB* blood group genotypes were directly determined, based on the molecular size of allele-specific amplification products. The analysis of nucleotide sequence in three major subjects in the *cisAB* blood group revealed chimeric structures of the A allele and B allele on the same gene.

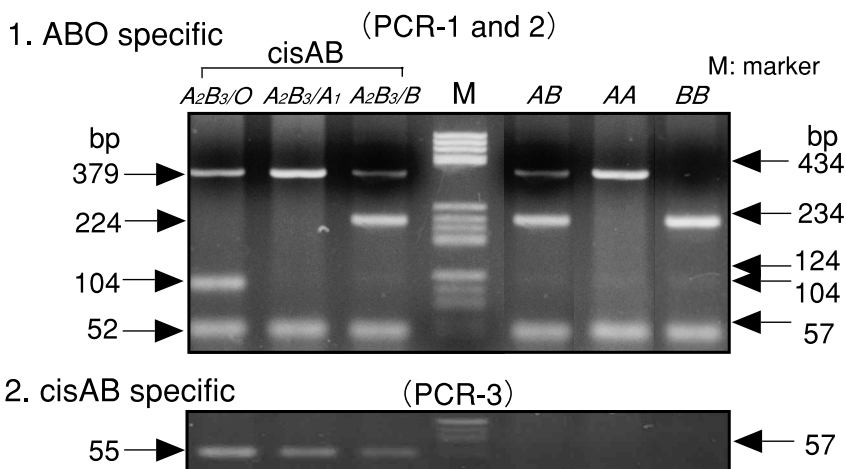


Figure 7. Electrophoretic patterns of PCR products in the three major *cisAB* genotypes. Genomic DNA extracted from leukocytes was amplified by PASA method using 5 primer sets (primer 1 and 2, primer 3 and 4, primer 5 and 6, primer 7 and 8, and primer 9 and 10). M, Hae III digest of Plasmid pBR322 (marker); upper panel: ABO allele specific; Lower panel: *cisAB* allele specific.

Table 5 Partterns of PASA method for all possible ABO genotypes

bp (Allele specific band)	<i>A/O</i>	<i>A/A</i>	<i>B/O</i>	<i>B/B</i>	<i>O/O</i>	<i>A/B</i>	<i>cisAB</i>		
							<i>A₂B₃/O</i>	<i>A₂B₃/A₁</i>	<i>A₂B₃/B</i>
(a) 379 (A,O specific)	+	+	+	-	+	+	+	+	+
(b) 224 (B specific)	-	-	+	+	-	+	-	-	+
(c) 104 (O specific)	+	-	+	-	+	-	+	-	-
(d) 52 (A,B specific)	+	+	+	+	-	+	+	+	+
(e) 55 (<i>cisAB</i> specific)	-	-	-	-	-	-	+	+	+

+, Presence of the expected specific ABO gene type fragment. -, Absence of the expected specific ABO gene type fragment. (a), Specific band A and O alleles by using primers (7 and 8). (b), Specific band B allele by using primers (5 and 6). (c), Specific band of O allele by using primers (1 and 2). (d), Specific band of A and B alleles by using primers (3 and 4). (e), Specific band of *cisAB* allele by using primers (9 and 10).

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