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ABO genotyping in leukemia patients reveals new *ABO* variant alleles

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ABSTRACT. The ABO blood group is the most important blood group system in transfusion medicine and organ transplantation. To date, more than 160 *ABO* alleles have been identified by molecular investigation. Almost all *ABO* genotyping studies have been performed in blood donors and families and for investigation of ABO subgroups detected serologically. The aim of the present study was to perform *ABO* genotyping in patients with leukemia. Blood samples were collected from 108 Brazilian patients with chronic myeloid leukemia (N = 69), chronic lymphoid leukemia (N = 13), acute myeloid leukemia (N = 15), and acute lymphoid leukemia (N = 11). *ABO* genotyping was carried out using allele specific primer polymerase chain reaction followed by DNA sequencing. *ABO*O01* was the most common allele found, followed by *ABO*O22* and by *ABO*A103*. We identified 22 new *ABO*$_{variants}$* in the coding region of the *ABO* gene in 25 individuals with leukemia (23.2%). The majority of ABO variants was detected in *O* alleles (15/60.0%). In 5 of 51 samples typed as blood group O (9.8%), we found non-deletional *ABO*O* alleles. Elucidation of the diversity of this gene in leukemia and in other diseases is important for the determination of the effect of changes in an amino

acid residue on the specificity and activity of ABO glycosyltransferases and their function. In conclusion, this is the first report of a large number of patients with leukemia genotyped for *ABO*. The findings of this study indicate that there is a high level of recombinant activity in the *ABO* gene in leukemia patients, revealing new ABO variants.

Key words: ABO blood group; DNA polymorphism; Leukemia; Genetic polymorphism; *ABO* gene; Brazilian population

INTRODUCTION

The ABO blood group is the most important blood group system in transfusion medicine and organ transplantation. Using classical serological studies, it is possible to classify individuals into four blood groups (A, B, O, and AB). Numerous phenotypes with weak expression of A and B on red cells have been detected and different terminologies have been adopted for ABO subgroup classification (Issitt and Anstee, 1998).

The sequence of nucleotides comprising the *ABO* gene, its structure and some of its common variants were determined in the early 1990s (Yamamoto and Hakomori, 1990; Yamamoto et al., 1990a). This gene, mapped on chromosome 9q34.1-34.2, consists of 7 exons ranging from 28 to 688 bp. More than 90% of the coding sequence is located in exons 6 and 7, and contains the catalytic domain (Yamamoto, 2001). The *ABO*A101* is considered the reference sequence, to which other *ABO* alleles are compared. The *ABO*B101* allele is distinguishable from *ABO*A101* at eight nucleotide (nt) positions, which result in four amino acid changes in the expressed protein. Among these, substitutions responsible for alterations at two sites (L266M and G268A) determine the A or B specificity of the enzyme (Yamamoto, 2004).

The single nucleotide deletion at 261 of exon 6, found in a large number of *O* alleles, is responsible for the loss of the activity of the enzyme (Yamamoto et al., 1990b).

To date, more than 160 *ABO* alleles have been reported in the literature. Many of them encode glycosyltransferases with change in activity and/or specificity (Yamamoto, 2004).

Although the function of ABO antigens has not been established yet, associations between ABO blood groups and certain diseases have been described. These include the association between blood group O individuals with increased incidence of duodenal ulcers and gastric carcinoma (Daniels, 2002). Aberrant expression of ABO antigens has been reported in pre-malignant and in malignant cells. The weakness of ABO antigens in leukemia patients has been reported mainly by serological analysis in individual case reports, especially in the myeloid lineage, or in small numbers of samples (Kolins et al., 1978; Matsuki et al., 1992).

Almost all *ABO* genotyping studies have been performed in blood donors and families and for investigation of ABO subgroups detected serologically. Hence, we studied the ABO blood groups among patients with leukemia using conventional ABO typing, allele specific primer polymerase chain reaction (PCR-ASP) and DNA sequencing.

PATIENTS AND METHODS

This prospective study was conducted at Hospital das Clínicas da Universidade de São Paulo, in São Paulo, Brazil. São Paulo City is the capital of the State of São Paulo in Southeast

Brazil. It is located at 23°32'36", 46°37'59"W. The city has a population of just over 11 million, which makes it the most populous in the southern hemisphere (IBGE, 2005).

Venous blood samples from 108 unrelated Brazilian patients with chronic myeloid leukemia (N = 69), chronic lymphoid leukemia (N = 13), acute myeloid leukemia (N = 15), and acute lymphoid leukemia (N = 11) were drawn for ABO erythrocyte phenotyping and ABO genotype determination.

All participants of this survey (51 males, 57 females) were tested for ABO typing either serologically or molecularly. The mean age of patients was 43.4 (range 15-85) years.

The institutional review board and the Ethics Committee of the Hospital das Clínicas da Universidade de São Paulo and of Fundação Pró-Sangue/Hemocentro de São Paulo approved this study, and all patients gave informed consent prior to the collection of samples.

ABO blood group typing and subgroup detection

ABO typing was determined by agglutination tests on washed erythrocytes using conventional tube test technique and gel test (DiaMed Latin America, Lagoa Santa, MG, Brazil) as described previously. The ABO subgroups were classified according to current recommendations (Brecher, 2005). The following commercial antisera and lectins were used for ABO typing and subgroup determination: monoclonal anti-A, anti-B and AB (DiaMed Latino America), polyclonal anti-A, anti-B, anti-AB (Fresenius Hemocare, SP, Brazil), and lectin anti-A1 and monoclonal anti-H (Gamma Biologicals, Houston, TX, USA). All reagents were used as recommended by the manufacturer's instructions. ABO reverse typing was conducted by agglutination testing and gel test using A_1, A_2, O, and B red blood cell suspension (DiaMed Latino America).

ABO genotyping by PCR-ASP technique

Blood samples and DNA preparation

Genomic DNA was extracted from whole blood with QIAamp® DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany). ABO genotyping was performed using PCR-ASP technique (Seltsam et al., 2003a). Amplification was performed for each sample to detect the presence or absence of 18 known polymorphic sites in exons 6 and 7 of *ABO* gene (261, 297, 467, 526, 564, 641, 646, 657, 669, 681, 771, 803, 829, 871, 930, 1009, 1054, and 1060). Each primer pair consisted of a primer specific for either the mutation or reference nucleotide at the respective position and a non-allele specific consensus primer. This approach was used to ensure that amplifications are independent from cis/trans linkages (Seltsam et al., 2003b). PCR mixtures contained 100 ng genomic DNA, PCR buffer (10 mM Tris-HCl, pH 8.3, 50 mM KCl, 1.5 mM $MgCl_2$), 100 µM of each dNTP, 5.0 pmol of each specific primer, and 0.5 U Taq DNA polymerase (Platinum Taq, Invitrogen, USA) in a final volume of 25 µL. All amplifications were performed in a Touchgene Gradient Thermal Cycler (Techne, USA). After initial denaturation at 94°C for 2 min, the samples were subjected to 30 cycles, consisting of 10 two-temperature cycles for 10 s at 94°C and for 60 s at 65°C, followed by 20 three-temperature cycles for 20 s at 94°C, for 50 s at 61°C and for 30 s at 72°C. PCR products were separated electrophoretically using 2.5%

agarose gels containing ethidium bromide (0.2 µg/mL) at 100 V for 60 min and visualized under UV irradiation.

Sequencing of PCR products

Amplification of a generic 1963-bp fragment spanning from intron 5 (nt 533-551) to 3' UTR nt 5-22 of the *ABO* gene and direct sequencing of exons 6 and 7 were done as follows: 100 ng genomic DNA, 2.5 mM $MgCl_2$, 0.2 mM dNTP, 5.0 pmol of each primer, 1.5 units DNA polymerase (Platinum Taq, Invitrogen, USA), and its supplied PCR buffer (Invitrogen, USA) in a 20-µL final volume. PCR was performed in a T3 Biometra Thermocycler (Biometra, Denmark) (Seltsam et al, 2003a). Initially, both *ABO* alleles were amplified simultaneously using primers for generic nucleotide sequencing (Seltsam, 2003a). The PCR products were then subsequently sequenced to identify all polymorphic sites in this region. Several nested primers were used for sequencing in accordance with the detected mutations to define the cis/trans linkage of the polymorphic sites using primer-specific primer pairs (haplotype specific nucleotide sequencing). The PCR products were purified using Exosap IT (USB, Amersham Biosciences, USA). DNA sequencing was performed using Big Dye Terminator Cycle Sequencing Standard Reagents Kit - version 3.1 (Applied Biosystems, USA). The reactions were performed according to the manufacturer's instructions using nested primers spanning from intron 5 to UTR 3' in an ABI Prism 770 Genetic Analyzer equipment (Applied Biosystems, USA).

Classification and nomenclature of *ABO* alleles

The known *ABO* alleles were named according to the nomenclature used in the Blood Group Antigen Gene Mutation Database (http://www.ncbi.nlm.nih.gov/projects/mhc/xslcgi.fcgi? cmd= bgmut/home).

RESULTS

ABO serological typing results according to leukemia type are presented in Table 1. The ABO phenotype most observed in patients with leukemia was blood type O in all groups studied (47.2%). After ABO subgroup investigation serologically, we found A_2 subgroup in 30.2% of patients with leukemia typed as blood group A.

Table 1. Distribution of leukemia type according to ABO serological typing results.

Leukemia type	CML (N = 69)	P	AML (N = 11)	P	CLL (N = 13)	P	ALL (N = 15)	P	Overall (N = 108)
ABO group									
O	30 (43.5%)	0.29	4 (36.4%)	0.44	9 (69.2%)	0.09	8 (53.3%)	0.60	51 (47.2%)
A_1	23 (33.3%)	0.08	3 (27.3%)	0.96	0 (0.0%)	0.01	4 (26.7%)	0.91	30 (27.8%)
A_2	9 (13.0%)	0.66	2 (18.2%)	0.50	1 (7.7%)	0.69	1 (6.7%)	0.49	13 (12.0%)
B	5 (7.2%)	0.33	1 (9.1%)	0.98	2 (15.4%)	0.41	2 (13.4%)	0.55	10 (9.3%)
AB	2 (2.9%)	0.55	1 (9.1%)	0.32	1 (7.7%)	0.41	0 (0.0%)	0.41	4 (3.7%)

Data are reported as number of individuals tested, with percent in parentheses. CML = chronic myeloid leukemia; AML = acute myeloid leukemia; CLL = chronic lymphoid leukemia; ALL = acute lymphoid leukemia.
*P < 0.05.

ABO genotype was initially determined in 60 patients (55.5%) using PCR-ASP. After DNA sequencing, *ABO* genotyping was confirmed in additional 23 samples, totaling 83 (76.8%), shown in Table 2. The most frequent A_1, A_2, *B*, and *O* alleles identified in this group of patients were *ABO*A103*, *ABO*A201*, *ABO*B101*, and *ABO*O01*, respectively.

Table 2. ABO serological typing and genotyping results in patients with leukemia after PCR-ASP and DNA sequencing (N = 108).

ABO phenotype	Genotype (*ABO**)	Number	Relative frequency
A_1 (N = 30)	*A101/001*	3	0.0277
	A101/A206	2	0.0185
	A102/O01	3	0.0277
	A102/O02	1	0.0093
	A102/O06	1	0.0093
	A102/A106	1	0.0093
	A103/O01	4	0.0370
	A103/O02	1	0.0093
	A103/O06	2	0.0185
	A103/O22	6	0.0555
	A_1*$_{variant}$	**6**	**0.0555**
A_2 (N = 13)	*A201/A201*	1	0.0093
	A201/A202	3	0.0277
	A201/A206	1	0.0093
	A201/O23	1	0.0093
	A201/O01	2	0.0185
	A202/O21	1	0.0093
	A202/O23	1	0.0093
	A205/O01	1	0.0093
	A_2*$_{variant}$	**2**	**0.0185**
B (N = 10)	*B101/O01*	5	0.0463
	B101/O02	3	0.0277
	B*$_{variant}$	**2**	0.0185
AB (N = 4)	*A102/B101*	2	0.0185
	A102/B103	1	0.0093
	A103/Bx01	1	0.0093
O (N = 51)	*O01/O01*	8	0.0741
	O01/O02	4	0.0370
	O01/O05	6	0.0555
	O01/O06	2	0.0185
	O01/O07	1	0.0093
	O01/O22	6	0.0555
	O05/O05	3	0.0277
	O05/O06	1	0.0093
	O06/O06	1	0.0093
	O06/O22	4	0.0370
	O*$_{variant}$	**15**	**0.1389**

*Boldface type is used to designate the new *ABO* alleles identified in this study.

In our study, *ABO*O01* was the most common allele found, with a relative frequency of 0.5737, followed by *ABO*O22* (0.1480) and by *ABO*A103* (0.1296). We identified 22 new *ABO*$_{variants}$* in the coding region of the *ABO* gene in 25 individuals with leukemia (23.2%) (Table

3). The new ABO variants consisted of 11 single nucleotide substitutions (414G>C, 483C>A, 520C>G, 668G>T, 895G>T, 907G>C, 959C>T, 1038G>A, 1055G>C, 1057A>G, and 1059C>A), 12 single base insertions (667insT, 734insC, 856insA, 857insA, 858insG, 959insT, 960insC, 986insT, 1012insA, 1049insG, 1050insG, and 1052insT), 6 base deletions (465delG, 507delG, 547delG, 899delG, 904delG, and 1010delG), and one reciprocal translocation (1000G>C, 1001C>G) located within exon 7. The majority of ABO variants were detected in *O* alleles. In 5 of 51 samples typed as blood group O (9.8%) we found non-deletional *ABO*O* alleles. The 1019G>A in exon 7 of the *ABO* gene detected in 5 samples was the most frequent mutation detected in the new ABO variants. The number of mutations identified by sequencing for each new $ABO_{variant}$ ranged from 1 to 8 (mean = 4.0 ± 2.2) (Table 3).

When serological results were compared to molecular analysis, all results except two were concordant. One sample was typed as blood group A_1, but molecularly genotyped as *ABO*A101/A206*. It is interesting to note that a sample classified serologically as group AB was shown to be *ABO*A103/ABO*Bx01* after DNA sequencing. In this sample, B antigen reactivity against anti-B sera was unaffected when tested with different anti-B sera.

Table 3. Exon mutations of the new *ABO* alleles detected in the present study.

ABO phenotype	Name Alias	Nucleotide change	Amino acid change	Number
A_1	$A1_{var1}$	467C>T;771C>T;829G>A	P156L; V277M	2
	$A1_{var2}$	467C>T;904delG	P156L; D302T	1
	$A1_{var3}$	547delG;959C>T	D183T; S320F	1
	$A1_{var4}$	856insA	None	1
	$A1_{var5}$	986insT	None	1
A_2	$A2_{var2}$	467C>T;1050insG	P156L; none	1
	$A2_{var1}$	1000G>C;1001C>G;1055G>C; 1057^{A}>G;1059C>A	A334R; R352P; N353E	1
B	$B1_{var1}$	297^{A}>G;771C>T;829G>A; 858insG;895G>T;899delG	V277M; W300C	1
	$B1_{var2}$	657C>T;703G>A;796delC; 803G>C;930G>A	G235S; G268A	1
O	O_{var1}	261delG;297^{A}>G;414G>C;646T>A; 681G>A;771C>T;829G>A	88fs+truncation	2
	O_{var2}	261delG;297^{A}>G;465delG;483C>A; 768C>A;907G>C;959insT;960insC	88fs+truncation	1
	O_{var3}	261delG;297^{A}>G;467C>T;1050insG	88fs+truncation	1
	O_{var4}	261delG;297^{A}>G;646T>A;667insT; 668G>T;681G>A;771C>T;829G>A	88fs+truncation	1
	O_{var5}	261delG;297^{A}>G;646T>A;771C>T; 829G>A;1019G>A	88fs+truncation	1
	O_{var6}	261delG;520G>A;734insC	88fs+truncation	1
	O_{var7}	261delG;547delG;959C>T	88fs+truncation	1
	O_{var8}	261delG;646T>A;681G>A;771C>T; 829G>A;1019G>A	88fs+truncation	1
	O_{var9}	261delG;1010delG;1019G>A;1050insG	88fs+truncation	1
	O_{var10}	297^{A}>G;507delG;526C>G;802G>A; 1012insA;1038G>A	Q169H; R176G; G268R; none; none	1
	O_{var11}	297^{A}>G;857insA	None	1
	O_{var12}	467C>T;1049insG	P156L; none	1
	O_{var13}	1019G>A;1052insT	R340K	2

DISCUSSION

ABO antigens are widely expressed in human tissues. Ichikawa et al. (1998) have demonstrated that the membrane glycoproteins which carry ABO antigens are important for growth regulation, such as the endothelial growth factor receptor and integrin receptors. These antigens are known to undergo drastic changes during maturation of cells in the epithelial and the erythroid lineages (Hakomori, 1999). Indeed, ABO mRNA gene has been demonstrated even in hematopoietic stem cells. Consequently, any event in these cells could lead to *ABO* gene alteration (Hosoi et al., 1998).

Critical mutations for *A* and *B* alleles have been found predominantly in exons 6 and 7 of the *ABO* gene, where the catalytic domain of ABO glycosyltransferases is encoded (Olsson and Chester, 2001; Downing and Darke, 2003). In this study, we typed for ABO and genotyped exons 6 and 7 of the *ABO* gene, using PCR-ASP and DNA sequencing, in 108 patients with leukemia to identify variations and polymorphisms.

The most common *ABO* allele found in our study, as well as in series testing blood donors, was *ABO*O01* (Batissoco et al., 2001; Olsson and Chester, 2001; Hosseini-Maaf et al., 2005). Although *ABO*A103* has been reported as a rare allele, it was the most detected A_1 allele (0.1296); *ABO*A102* (0.0834) and *ABO*A101* (0.0462), while common in different populations (Yip, 2002), were less identified in the group of patients reported here.

Bianco et al. (2001), using PCR-RFLP and flow cytometry, studied 57 patients with leukemia and showed that the loss of A and B antigens is common in patients with myeloid malignancies (28%).

Here, we report 20 known and 22 new ABO variants, the majority of them in the *O* allele. In 9.8% of the samples typed as blood group O, we found non-deletional *ABO*O* alleles. The sample O_{var10} has the mutation at 802 which is known to abolish the enzymatic activity of the ABO glycosyltransferase. These unusual *O* alleles lacking the common 261delG show a serious risk for erroneous interpretation in ABO genotyping (Hosseini-Maaf et al., 2005).

Interestingly, a sample typed serologically as blood group O, showed inconclusive ABO PCR-ASP genotyping. After DNA sequencing, it was possible to detect a reciprocal translocation in exon 7 (Table 3).

The detection of new alleles has proved helpful for determining the functional relevance of the different amino acid positions (Yip, 2002). These mutations, especially in hybrid alleles, could explain the different substrate specificity of the A and B enzymes, to better understand the inactivity of the *O* allele (Seltsam et al., 2003b; Sousa et al., 2005). Therefore, systematic ABO genotyping in different patient groups will presumably lead to the discovery of more ABO variants.

The high number of polymorphisms at the *ABO* gene may be due to different molecular mechanisms (Yamamoto, 2004) as shown in this study. As ABO antigens are expressed in stem cells, the alleles detected in leukemia patients, especially $ABO_{variants}$, may reflect a disruption in the hematopoiesis process. Elucidation of the diversity of this gene in leukemia and in other diseases, where alteration in ABO expression has been described, is important for the determination of the effect of changes in an amino acid residue on the specificity and activity of ABO glycosyltransferases and their functional relevance in diseases and in other circumstances.

In conclusion, this is the first report of a large number of samples of patients with leukemia genotyped for *ABO*. The findings of this study indicate that there is a high level of recombinant activity in the *ABO* gene in leukemia patients, revealing new ABO variants.

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