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Human genetic characterization: the analysis of phenotypic and genotypic profile through abo and rh blood group systems distribution in south Brazil

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Abstract
The search for understanding the population dynamics of genes and blood group genotypes in the ABO / Rh system is an important field of Population Genetics. Thus, this study aimed to identify genetic variability; phenotypic, allelic and genotypic frequencies of the ABO and Rh blood group systems and compare de number of blood donations performed in the south Brazil region. In order to determine and analyze the occurrence of the main phenotypic, genotypic and allele classes related to the ABO / Rh blood system, data collection was performed, referring to 64,066 blood donors who donated during the period from over 10 years. The population genetic profile analysis was performed based on the principles of Hardy-Weinberg equilibrium theorem the distribution of ABO blood group system observed was: O> A> B> AB. O represents 50.15% of donors, A represents 36, 11%, B represents 10.14% and AB only 3.58%. The phenotypic frequency for each one of these groups is: O = 0.5015, A = 0.3611, B = 0.1014 and AB = 0.0358. Regarding genotypic frequency, the homozygous genotype (ii) for type O prevailed, with 0.5016 (50.16%). For blood types A and B, heterozygous genotypes are more frequent, I^A i and I^Bi frequencies were 0.1582 (15.82%) and 0.0503 (5.03%), respectively. A and B Homozygotes have a reduced frequency, with I^A I^A 0.0499 (4.99%) and I^B I^B 0.0051 (0.51%). The genotype for type AB (I^A I^B) has the frequency 0.0158 (1.25%). Among donors, Rh positive blood type predominated with a total of 55,551 people, with a phenotypic frequency of 0.8670 (86.70%), while Rh negative blood group was present in 8,515 donors only, with a phenotypic frequency of 0,1329 (13.29%). The analysis of interaction between the two studied blood group systems (ABO and Rh) made possible to verify the percentage of each type of heterozygote present in the data. In this way, 68% were I^Ai/Dd, 21.6% were I^Bi/Dd. and 6.86% were I^AI^B/Dd. These data analyses together are helpful in understanding the differentiation of blood group loci and for designing prospective studies for establishing the associations of these loci with health variables in the populations studied.

Keywords: ABO, Rh, allele frequency, gene diversity, south Brazil

1. Introduction
Red blood cells carry membrane proteins and glycoproteins that act as erythrocytes antigens. About 700 antigens have been described. These antigens are organized in 36 blood groups recognized by the International Society of Blood Transfusion (ISBT) [1, 2]. Karl Landsteiner found three different blood types that were described as A, B, and O blood groups in 1900. Alfred Von Decastello and Adrian Sturli discovered the fourth type AB in 1902. In 1940, Karl Landsteiner, with Alexander Salomon Wiener, discovered the Rhesus (Rh) factor. The blood systems identification has promoted advances in blood transfusion medicine that allowed the development of many discoveries in Genetics, Immunology and Heamatology [3].

The ABO system is controlled by two genetic loci. The fut1 locus is located in 19th chromosome and encodes the H substrate, by producing a fucosyltransferase protein that attaches L-fucose sugar in a membrane protein. The abo locus is situated on the long arm of 9th chromosome. The IA allele encodes an N acetylgalactosamine transferase (A trasferase) that adds an N acetylgalactosamine to H substrate, creatting the A antigen. The IB allele encodes an N acetylglucosamine transferase (B trasferase) that adds an N acetylglucosamine to H substrate creating the B antigen. The i allele encondes a nonfunctional transferase, that do not originated antigenic protein. So, the four ABO phenotipes A, AB, B, and O are determined on the basis of presence or absence of A and B antigens. The IA IA and IA i, IB IB and IB i and i i genotypes are correlated with A, B and O phenotypes respectively [2, 4]. The antigens of the Rh system are encoded by two closely link genes (rhd and rhce) that are sited on the short arm of the 1st chromosome and are genetically independent of the ABO system [5]. The rhd allele encodes the RhD, the most imunogenic antigen, so the Rh factor term refers only to RhD antigen. Rh+ refers the presence of RhD protein in cell membrane and Rh -, this absence [6,7].

Human populations share the same ABO and Rh blood group systems. However, the proportions of these blood groups show variation across geographic locations. Population genetics studies using these systems of blood groups in different countries indicate the phenotypic differences and estimate the frequency of alleles in different populations, which shows the wide variety present in the countries with high rates of mixing and migration, such as Brazil [8].

A specific population is genetically defined by the sum of allelos frequencies, a parameter that allows to know the rage of variability or heretozigosys of population [7].

The variability of ABO and Rh has directed various

researches and several correlations have been made. It is known, for example, about the association of such blood-grouping systems with diseases such as Chagas disease, Pierre Robin syndrome, cardiovascular diseases, HIV, hepatitis B, breast cancer, diabetes mellitus, stomach ulcers, among other [3, 6, 9, 10, 11].

Knowledge of the phenotypic and genotypic distribution, besides specific needs of each region of the country contributes to effective management of blood banks and also to safer transfusions [12]. Based on this theme, this research aimed to identify genetic variability; phenotypic, allelic and genotypic frequencies of the ABO and Rh blood group systems and compare de number of blood donations performed in the central western region of the state of Paraná, Brazil, over 10 years.

2. Materials and Methods

This study was approved by the Ethics and Research Committee of the State Health Department of Paraná – Workers´ Hospital (CEP SESA - HT) in Curitiba, Paraná, No. 2,316,870.

Data regarding donations that were made at Hemonucleus from Campo Mourão, Paraná, Brazil, which belongs to the Hemepar network and supplies hospitals throughout the Campo Mourão Region Community (COMCAM), were available by the Hemotherapeutic Information and Control System of Paraná (SHTWEB). Data contain information about the number of donations of each blood type (ABO and Rh) between 2007 and 2017, without identifying the volunteers and any kind of distinction between them.

The population genetic profile analysis was performed based on the principles of Hardy-Weinberg equilibrium theorem. Data were analyzed by descriptive statistical in Microsoft Excel®. Measures such as percentage and confidence interval were applied to identify relationship between the variables.

Allele frequencies were calculated under the assumption of Hardy-Weinberg equilibrium and results were expressed as percentages, using the following equations:

Hardy-Weinberg equilibrium: $(p+q+r)2 = 1$ and, to obtain the frequency of the O allele, it is enough to extract the square root of observed frequency of individuals from group O, since $r = \sqrt{r2} = \sqrt{O}$. After that, it is need to calculate:

$p = 1-\sqrt{B+O} = 1-\sqrt{q2 +2qr + r2} = 1- (q+r)$

$q = 1-\sqrt{A+O} = 1-\sqrt{p2 +2pr + r2} = 1- (p+r)$

Since the sum of these estimates rarely gives a value exactly equal to 1, they are called preliminary estimates and are represented by p', q' and r'. To correct them, it is need to calculate the deviation (D) between the unit and the sum of the estimates, that is, it is necessary to obtain:

$D = 1 – (p'+ q'+ r')$

And calculate the corrected estimates p, q and r by:

$p= p´(1 + D/2)$

$q=q´(1 + D/2)$

$r= (r´+ D/2) (1+D/2)$ ou $r=1 – (p+q)$

Where p, q and r represents the frequencies of the genes for A, B, O, Rh+, and Rh−, respectively [13].

The comparison between the number of donations over the years and also between the number of donations at each time of the year was performed and the results obtained are showed as percentage. Population data for COMCAM region were obtained from Brazilian Institute of Geography and Statistics (IBGE) Population Estimate, 2017 [14].

3. Results & Discussion

3.1 ABO blood group system

Among 64,066 blood donations, collected from 2007 to 2017, the distribution of ABO blood group system observed was: O> A> B> AB. O represents 50.15% of donors, A represents 36, 11%, B represents 10.14% and AB only 3.58%. The phenotypic frequency for each one of these groups is: O = 0.5015, A = 0.3611, B = 0.1014 and AB = 0.0358 (Table 1).

Table 1: Phenotypic distribution of ABO blood group system of blood donors from Campo Mourão-PR from 2007 to 2017 and city´s population estimate.

ABO System	Number of people	Phenotypic Frequency	%	Population estimate
O	32132	0,5015	50,15	47.247
A	23137	0,3611	36,11	34.019
B	6501	0,1014	10,14	9.553
AB	2296	0,0358	3,58	3.372
Total	64066	0,9998	99,98	94.191

Regarding genotypic frequency, the homozygous genotype (ii) for type O prevailed, with 0.5016 (50.16%). For blood types A and B, heterozygous genotypes are more frequent, I^A i and I^Bi frequencies were 0.1582 (15.82%) and 0.0503 (5.03%), respectively. A and B Homozygotes have a reduced frequency, with I^A I^A 0.0499 (4.99%) and I^B I^B 0.0051 (0.51%). The genotype for type AB (I^A I^B) has the frequency 0.0158 (1.25%) (Table 2).

The frequency of alleles responsible for the ABO blood group system was: i = 0.7083 (70.83%), I^A= 0.2234 (22.34%) and I^B= 0.0711 (7.11%) (Table 2).

Table 2: ABO genotype and allele frequency found among blood donors from Campo Mourão-PR from 2007 to 2017.

Genotype	Genotypic frequency	%	Pop. Est.	Alleles	Allele Frequency	%	Pop. Est.
I^A I^A	0,0499	4,99	4.701	I^A	0,2234	22,34	21.046
I^A i	0,1582	15,82	14.904	I^B	0,0711	7,11	6.698
I^B I^B	0,0051	0,51	480	i	0,7083	70,83	66.730
I^B i	0,0503	5,03	4.738				
I^A I^B	0,0158	1,58	1.488				
i i	0,5016	50,16	47.256				
Total	0,7809	78,09	73.567		1,0028	100,28	94.474

3.2 Rh blood group systems

Among donors, Rh positive blood type predominated with a total of 55,551 people, with a phenotypic frequency of 0.8670 (86.70%), while Rh negative blood group was present in 8,515 donors only, with a phenotypic frequency of 0,1329 (13.29%) (Table 3).

Table 3: Phenotypic distribution of the Rh blood group system of blood donors in the city of Campo Mourão-PR from 2007 to 2017.

Blood type	Nº of people	Phenotypic Frequency	%	Pop. Est.
Positive Rh	55551	0,8670	86,70	81.687
Negative Rh	8515	0,1330	13,30	12.530
Total	64.066	1	100	94.217

Regarding genotypic frequency, the dominant homozygous genotype (DD) responsible for positive Rh phenotype appeared most frequently, with 0.4038, followed by heterozygous genotype (Dd) for positive Rh phenotype, with 0.2316, and finally, the recessive homozygote (dd) for

negative Rh phenotype, with 0.1328. The frequency of alleles D and d were, respectively: 0.6355 (63.55%) and 0.3645 (36.45%) (Table 4).

Table 4: Genotype and allele frequency of Rh system found among blood donors from Campo Mourão-PR from 2007 to 2017.

Genotype	Genotypic Frequency	%	Pop. Est.	Allele	Allele Frequency	%	Pop. Est.
DD	0,4038	40,38	38.042	D	0,6355	63,55	59.871
Dd	0,2316	23,16	21.819	d	0,3645	36,45	34.340
dd	0,1328	13,28	12.511				
Total	0,7682	76,82	72.372		1	100	94.211

3.3 Heterozygosis

The analysis of interaction between the two studied blood group systems (ABO and Rh) made possible to verify the percentage of each type of heterozygote present in the data. In this way, 68% were I^Ai/Dd, 21.6% were I^Bi/Dd. and 6.86% were I^AI^B/Dd (Table 5).

Table 5: Distribution of heterozygotes for ABO and Rh systems among blood donors from Campo Mourão-PR from 2007 to 2017.

Genotype	%	Population Estimative
I^A i/Dd	68%	64.064
I^B i/Dd	21,6%	20.349
I^A I^B/Dd	6,86%	6.462
Total	96,46	90.875

3.4 Number of Donations

The number of donations between 2007 and 2017 increased gradually, except in 2013, when the number of donations decreased (Table 6). From 2007 to 2017 the number of donations increased 53.79%.

Table 6: Number of donations from 2007 to 2017 at Hemonucleus of Campo Mourão-Paraná.

Year	Number of Donations
2007	4811
2008	5075
2009	5178
2010	5442
2011	5528
2012	5606
2013	5123
2014	5846
2015	6651
2016	7230
2017	7399

Throughout each year, the percentage of donations for each month was evaluated. November generally was the month in which most donations were made. The month with the least donations was December (Table 7).

Table 7: Percentage of donations in each month from 2007 to 2017.

Year	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
2007	5,96	8,50	8,12	9,62	7,79	7,56	7,52	8,97	9,85	8,21	13,28	4,57
2008	8,78	8,88	5,95	8,25	6,81	10,34	8,29	6,16	6	11,11	12,47	6,89
2009	5,07	9,36	7,01	7,91	8,32	10,46	8,70	9,90	10	6,10	11,43	5,67
2010	7,05	7,99	9,95	9,70	9,97	6,57	8,61	7,49	6,22	7,80	10,85	7,71
2011	9,87	8,48	8,64	6,47	8,61	9,40	9,35	8,10	9,64	6,92	7,23	7,23
2012	4,92	7,68	9,91	8,59	7,72	8,38	7,72	9,65	9,36	9,81	9,95	6,26
2013	4,47	8,27	8,31	6,59	8,43	6,44	7,72	9,68	11	8,43	10,11	10,50
2014	7,33	7,45	8,60	7,28	8,77	7,32	10,55	8,58	8,31	10,24	7,45	8,05
2015	7,15	5,62	9,38	7,32	8,65	8,43	10,90	9,87	7,47	9,75	9,69	5,71
2016	8,17	7,60	9,62	6,79	7,81	8,99	8,85	8,99	9,69	7,16	9,30	6,98
2017	11,04	6,91	10,73	7,48	8,04	9,06	7,12	7,20	7,24	7,86	10,65	6,62

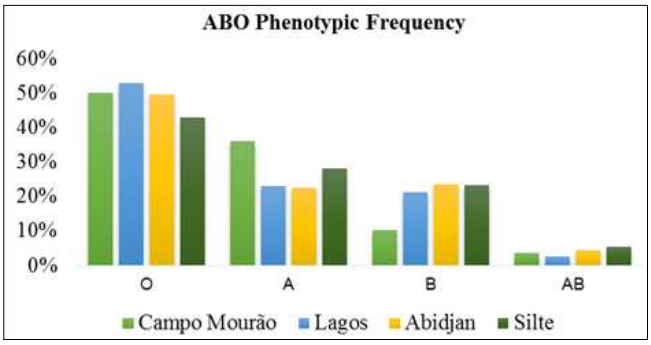
3.5 Discussion

By analyzing the frequency and phenotypic distribution of ABO blood group system among donors from Hemonucleus of Campo Mourão, it appears that there is a phenotypic pattern that may be represented as follows: O> A> B> AB.

The results obtained in Campo Mourão (O = 0.5015 (50.15%), A = 0.3611 (36.11%), B = 0.1014 (10.14%) and AB = 0.0358 (3, 58%) resemble the results of other surveys conducted in different regions of Brazil, for example cities of Mato Grosso State, such as Primavera do Leste, where the frequency and estimated phenotypic distribution was O = 0.4852 (48, 52%), A = 0.3612 (36.11%), B = 0.1174 (11.74%) and AB = 0.0362 (3.62%) [15], and Rondonópolis (O = 0, 5369 (53.69%), A = 0.3179 (31.79%), B = 0.1091 (10.91%) and AB = 0.0361 (3.61%) [7].

Similar results were also found in cities of Maranhão State,

such as Peritó (O = 0.5257 (52.57%), A = 0.3257 (32.57%), B = 0.1228 (12.28%) and AB = 0.0257 (2, 57%)), in Vargem Grande (O = 0.5416 (54.16%), A = 0.3125 (31.25%), B = 0.1043 (10.43%) and AB = 0.416 (4.16%)), Miranda (O = 0.6143 (61.43%), A = 0.2699 (26.99%), B = 0.1048



(10.48%) and AB = 0.0110 (1.10%)), Saint Benedict (O = 0.5606 (56.06%), A = 0.2651 (26.51%), B = 0.1516 (15.16%) and AB = 0, 0227 (2.27%) and São Luís (O = 0.5372 (53.72%), A = 0.3354 (33.54 %), B = 0.0964 (9.64%) and AB = 0.0310 (3.10%)) [16] (Figure 1).

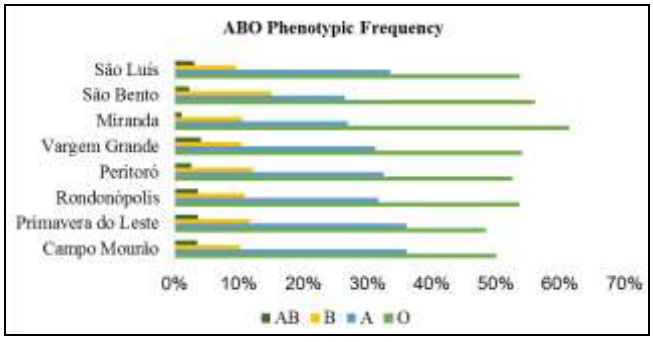


Fig 1: Graphical representation of the phenotypic distribution of ABO blood group system in some cities of Brazil.

Regarding the ABO phenotypic distribution, when compared to other regions of the world, Campo Mourão donors follow the same patterns found in other countries. In Lagos, Nigeria, group O also prevailed (52.90%), followed by A (23.10%), B (21.30%) and AB (2.70) [17]. In Abidjan, Côte d'Ivoire, the results are similar, with O representing 49.74% of people, A representing 22.51%, B 23.53% and AB 4.40% [18]. Finally, in Silte, Ethiopia, O obtained 43.08%, A 28.11%, B 23.35% and AB 5.44% [12] (Figure 2).

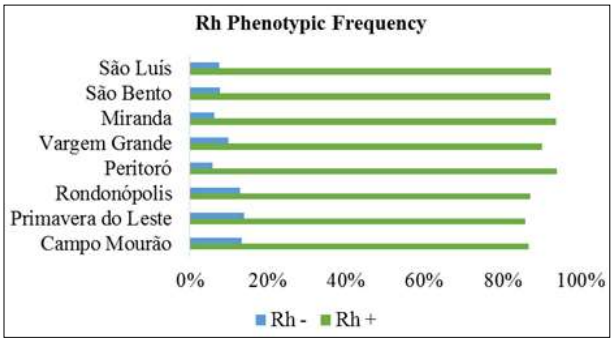


Fig 2: Graphical representation of phenotypic distribution of ABO blood group system in different countries.

According to Beiguelman [19], the distribution of ABO blood groups in Brazilian population is approximately: O 45% O, 42% A, 10% B and 3% AB, which shows that both small populations, such as Campo Mourão, as large populations as Brazil, follow the same patterns, which may be studied due to the knowledge about the inheritance of ABO blood group system [16].

Rh system, like ABO system, has its groups similarly distributed across populations. Among donors from Campo Mourão, 55,551 (86.70%) are Rh positive and 8515 (13.30%) are Rh negative, the phenotypic frequency are 0.8670 and 0.1330, respectively. In other cities the results were similar in relation to the predominance of positive Rh, even though there is a distinction between its phenotypic frequency: in Primavera do Leste, Rh+ is 85.93%, and its frequency 0.8593; and Rh- 14.07%, with frequency of 0.1407 [15]; in Rondonópolis, Rh+ is 87.10%, with the frequency of 0.8710 and Rh- is 12.90% with frequency 0.1290 [7] ; in Peritoró, Rh+ is 94%, frequency 0.9400, and Rh- is 6.01% with 0.0601; Vargem Grande, Rh+ is 90.10%, frequency 0.9010, and Rh- is 9.90%, frequency 0.0990; Miranda, Rh+ is 93.66%, with the frequency 0.9366, and Rh- is 6.34%, with frequency 0.0634; São Bento, Rh+ is 92.23%, frequency 0.9223, and Rh- is 7.77%, frequency 0.0777; São Luís, Rh+ is 92.42%, with the frequency of 0.9242, and Rh- is 7.58%, with frequency of 0.0758 [16] (Figure 3).

Comparing with other regions in the world, the predominance of Rh-positive phenotype was also observed. Both Lagos, Nigeria [17] and Abidjan, Côte d'Ivoire [18] obtained Rh+ = 97% and Rh- = 3%. In Silte, Ethiopia [12], the result varied; however, the pattern is the same, being Rh+ 92.06% and Rh- 7.94%

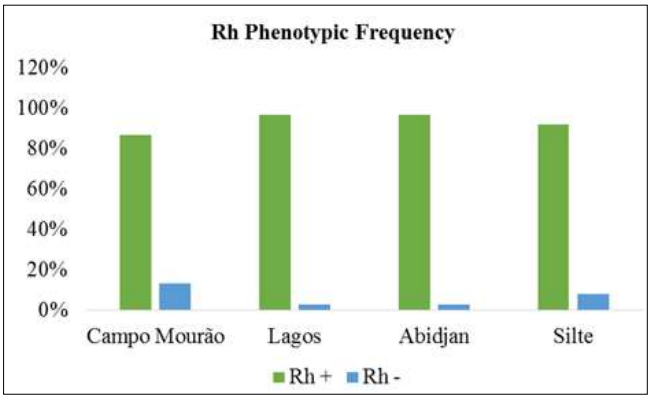


Fig 4: Graphical representation of phenotypic distribution of Rh blood group system in different countries.

4. Conclusions

Similar studies should be undertaken in mother regions of the country to establish the blood group distribution. Collectively these studies would provide the national blood bank services with critical information for supply forecasting and blood inventory management [2].

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