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BRIEF ARTICLE

Blood groups, hemoglobin phenotypes and clinical disorders of consanguineous Yansi population

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Abstract

AIM: To study frequency of blood groups, prevalence of sickle-cell anemia trait and glucose-6-phosphate dehydrogenase deficiency (G6PD), among consanguineous Yansi tribe.

METHODS: A total of 525 blood samples were collected, of which 256 among the Yansi population, and 269 for the unrelated control group in the Bandundu province of Democratic Republic of Congo. Blood group antigens were determined in the following systems: ABO, Rh, Kell, Duffy, Kidd and MNS. Blood grouping and extended phenotype tests were performed according to standard immunohematological procedures. Spot tests and tandem mass spectrometry were used respectively for the assessment of G6PD and sickle-cell anemia trait.

RESULTS: The frequency of ABO phenotypes conformed to the following order O>A>B>AB with notably 62.5%, 23.8%, 12.1% and 1.6% for the Yansi, and 54.6%, 27.5%, 14.1% and 3.7% for the unrelated control group, respectively (P = 0.19). As for the Rh phenotypes, the most frequent were ccD.ee, ccD.Ee, CcD.ee, corresponding to 71.5%, 12.1% and 12.1% for the Yansi, and 70.6%, 15.6% and 8.2%, for the unrelated control group (P = 0.27). The frequency of MN and Ss phenotypes were statistically different between groups (P = 0.0021 and P = 0.0006). G6PD was observed in 11.3% of subjects in the Yansi group, and in 12.4% of controls (P = 0.74). The sickle-cell anemia trait was present in 22.4% of Yansi subjects and 17.8% in the control group (P = 0.24). Miscarriages and deaths in young age were more common among Yansi people.

CONCLUSION: This study shows a significant difference in MNS blood group distribution between the Yansi tribe and a control population. The distribution of other blood groups and the prevalence of hemoglobinopathies did not differ in the Yansi tribe.

Key words: Blood group antigens; Blood group phenotype; Glucose-6-phosphate dehydrogenase deficiency; Sickle-cell anemia; Hemoglobin electrophoresis; Clinical disorders; Consanguinity; Yansi

Core tip: Assessment of blood group frequencies is important to evaluate the risk of alloimmunization after transfusion or pregnancy. Few documented studies have been published about the frequency of blood groups and extended phenotypes in the Congolese people in general and the consanguineous Yansi tribe in particular. This is also the case for the prevalence of glucose-6-phosphate dehydrogenase deficiency and sickle-cell trait. We show that the distribution of MNS blood groups is different in the Yansi tribe, compared to the general population. The Yansi also present with a higher frequency of medical disorders. This study may help in sensitizing the Congolese population about the medical risks associated with consanguineous unions and in building up a database of genetic diseases in the population.

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INTRODUCTION

The antigens of the ABO system were the first to be discovered among the blood group antigens and were known as the first human genetic markers[1]. Nowadays, there exist 308 antigens of red blood cells described in 30 systems, 12 collections, a 700 series, and a 901 series[2,3]. Apart from the ABO and Rh, there are many other systems of transfusion significance, such as Kell, Duffy, Kidd and MNS[4].

The blood groups antigens are most important in transfusion, pregnancy and transplantation because of their immunogenic capacity[5], and also in human genetics[6]. The frequency of blood groups antigens differs between populations[7].

A "genetic" population or a "mendelian" population is influenced by the way the procreating couples are constituted. It is characterized by a genetic pool and by cultural rules that govern the formation of those couples (rule of belonging to a community)[8]. The genes coding for the blood groups' markers are, like all genes, inherited from parents and their phenotypic expression is subjected to hereditary laws[9].

In the Yansi tribe from the Bandundu province in the Democratic Republic of Congo, the constitution of couples lies on two types of marriage: the ordinary marriage and the preferential or consanguineous marriage of "kitiul" type. Very few documented studies have been performed about the constitution of the preferential marriage among Yansi people. Mfukala and Hochegger mention nearly 60% of preferential marriages in which the grandfather marries his granddaughter to the son of his brother's daughter[10,11].

Consanguinity increases the probability that both spouses become heterozygote for the same recessive genes causing an increase of homozygosity for that gene in their descent[12,13]. Therefore, consanguinity increases the risk of developing genetic diseases such as hemoglobinopathies with the possibility of increasing the frequency of the deficient allele for glucose-6-phosphate dehydrogenase deficiency (G6PD)[14,15].

The G6PD deficiency is the most common enzymatic disorder in humans. It is a sex-linked genetic disease affecting more particularly African, Mediterranean, and Far Eastern people with an incidence of 25%[16].

The sickle-cell anemia is an example of recessive autosomic disease[17]. More than 90% of people with sickle-cell anemia are born in Africa where its prevalence varies in some regions between 10%-40%. In the Democratic Republic of Congo, prevalence of sickle-cell anemia trait varies between 15%-20%[18].

It is in this context that we have determined the frequency of antigens of ABO and Rh blood groups, and of the other blood systems such as Kell, Duffy, Kidd and MNS. We also evaluated the frequency of G6PD deficiency and sickle-cell anemia trait among the Yansi tribe practicing consanguineous marriage compared to an unrelated control group.

MATERIALS AND METHODS

A total of 525 blood samples were drawn, of which 256 among the consanguineous Yansi, and 269 among the control group. Subjects of all ages and of both sexes were selected in the scope of the study. The male/female ratio was not different with 44.9% and 52.4% of male subjects, 55.1% and 47.6% of female subjects in Yansi subjects and control group, respectively. The control subjects were younger than the Yansi subjects: the mean age was 40.86 ± 17.11 years (range: 3-79 years) in Yansi subjects and 28.87 ± 17.20 years (range: 0-79 years) in the control group. Our samples were collected in September 2010 and in June 2011 in the Bandundu province of Democratic Republic of Congo. The Yansi subjects were located in the district of Kwilu whereas control subjects where located in the city of Kikwit, both in the Bandundu province. Controls subjects did not belong to the Yansi tribe but lived in the same region of Congo. Information about subjects was collected through a questionnaire and blood samples were harvested for biological analyses.

For blood groups, samples were collected in EDTA tubes, whereas for G6PD and hemoglobin phenotypes, blood was collected on Whatman 903 filter paper. Blood grouping and extended phenotyping were achieved according to standard immunohematological procedures based on erythrocyte agglutination with specific antisera followed, when necessary, by the addition of antiglobulin reagent[19]. The tube technique was used for all analyzes of blood grouping using monoclonal and polyclonal reagents in accordance with manufacturer's procedures. The phenotypes ABO and D were performed by the

double method of Beth-Vincent and Simonin. The ABO and D antigens were typed using monoclonal antisera of Pelikloon (Sanquin). Typing of C, c, E, e, Fya, Fyb, Jka, Jkb, M antigens was carried out with antisera from Immundiagnostika (Seraglu) while K, N, S, s antigens were typed using antisera from Seraclone (Biotest).

The detection of the sickle-cell anemia trait was carried out by tandem mass spectrometry[20,21] whereas assessment of the rate of G6PD deficiency was measured by the Beutler fluorescent spot test technique[22]. The principle of determination of G6PD deficiency is based on the visualisation of nicotinamide adenine dinucleotide phosphate produced in a blood spot sample. The reagent is prepared by mixing glucose-6P, β-nicotinamide adenine dinucleotide phosphate, saponine, Tris HCl and glutathione (all from Sigma). The reaction is observed under a ultraviolet lamp on Greiner Plate 655191.

Results are presented as frequencies and comparisons of variables between groups were done by a χ^2 test. Results were considered significant at the 5% level ($P < 0.05$). Calculations were done using SAS® version 9.3 (SAS® Institute; Cary, NC, United States).

RESULTS

We have studied the frequency of blood phenotypes among the consanguineous Yansi population that was compared with a population of unrelated subjects. Concerning the ABO phenotype, the distribution did not differ between the two groups ($P = 0.19$). These frequencies were determined as follows for the phenotypes O, A, B and AB, respectively: 62.5%, 23.8%, 12.1% and 1.6%; for the Yansi; 54.7%, 27.5%, 14.1% and 3.7% for the control group (Table 1). In a study based on a cohort of 2536 blood benevolent donors in the Democratic Republic of Congo, the frequency of ABO phenotypes was O>A>B>AB with 1427 (56.3%) for O, 558 (22.0%) for A, 464 (18.3%) for B and 87 (3.4%) for AB[23]. Overall the comparison of these data with our control group did not present significant difference ($P = 0.12$) but there was a significant difference ($P = 0.024$) between the Yansi and blood donors such that the blood group O frequency was higher in the Yansi (62.5%).

The frequency of Rh phenotypes did not significantly differ ($P = 0.27$) between the Yansi and the control group (Table 1), ccD.ee: 71.5% and 70.6%; ccD.Ee: 12.1% and 15.6%; ccD.EE: 0% and 1.1%; CcD.ee: 12.1% and 8.2%; CcD.Ee: 1.2% and 0.4%; CCD.ee: 0.4% and 0.4%; ccddee: 2.7% and 3.7%, respectively. Both populations were 90% Rh positive with a predominance of ccD.ee subgroup. Rh negative subjects accounted for 2.7% among the Yansi and 3.7% in the control group. Few documented studies have been published about the frequency of RHD antigen and RH phenotypes in the Congolese people. Two studies carried out on blood donors report frequencies of 98.9% and 99.5% for RHD[23,24]. As for the RH Cc and Ee phenotypes, the frequencies reported in blood donors was ccD.ee: 69.1%; ccD.Ee: 14.2%; ccD.EE: 1.2%; CcD.ee: 13.7%; CcD.Ee: 1.5%; CCD.ee: 0.2% et ccddee 0.1%[22]. These data are significantly different from our results in Yansi and unrelated subjects ($P < 0.0001$). This can be explained by the small number of samples. Larger studies are needed for the constitution of a reliable database of ABO blood groups and Rh phenotype.

Table 1 ABO, Rh and other phenotype frequencies in Yansi population and control subjects *n* (%)

	Yansi *n* = 256	Control *n* = 269	*P* value
ABO phenotype			0.19
A	61 (23.8)	74 (27.5)	
B	31 (12.1)	38 (14.1)	
O	160 (62.5)	147 (54.7)	
AB	4 (1.6)	10 (3.7)	
Rh phenotype			0.27
ccD.ee	183 (71.5)	190 (70.6)	
ccD.Ee	31 (12.1)	42 (15.6)	
ccD.EE	0	3 (1.1)	
CcD.ee	31 (12.1)	22 (8.2)	
CcD.Ee	3 (1.2)	1 (0.4)	
CCD.ee	1 (0.4)	1 (0.4)	
ccddee	7 (2.7)	10 (3.7)	
Kell phenotype			
K+k-	0	0	
K+k+	0	0	
K-k+	256 (100)	269 (100)	
Duffy phenotype			
Fy (a+b+)	0	0	
Fy (a-b+)	0	0	
Fy (a+b-)	0	0	
Fy (a-b-)	256 (100)	269 (100)	
Kidd phenotype			0.096
Jk (a+b+)	96 (37.5)	81 (30.1)	
Jk (a+b-)	141 (55.1)	173 (64.3)	
Jk (a-b+)	19 (7.4)	15 (5.6)	
MN phenotype			0.0021
MM	94 (36.7)	124 (46.1)	
MN	123 (48.1)	89 (33.1)	
NN	39 (15.2)	56 (20.8)	
Ss phenotype			0.0006
SS	10 (3.9)	35 (13.0)	
Ss	39 (15.2)	38 (14.1)	
ss	204 (79.7)	187 (69.5)	
S-s-	3 (1.2)	9 (3.4)	

The determination of extended phenotypes focused on the frequency of the most immunogenic systems, such as Kell, Duffy, Kidd and MNS (Table 1). In both populations, all subjects were Kell negative. In the Duffy system, the Fy (a-b-) phenotype was found in all subjects in both groups. The prevalence of Kell and Duffy antigens, which are strongly immunogenic, is low in the Democratic Republic of Congo[23]. This is also the case of Africans who reach 98% kk, 2% Kk and rare cases for KK[25].

The frequencies of MN and Ss phenotypes presented a significant difference ($P = 0.0021$ and $P = 0.0006$) between the two groups. These frequencies were respectively in Yansi and unrelated subjects 36.7% *vs* 46.1% for the MM phenotype; 48.1% *vs* 33.1% for MN; 15.2% *vs* 20.8% for NN; 3.9% *vs* 13% for SS; 15.2% *vs* 14.1% for Ss and 79.7% *vs* 69.5% for ss (Table 1). The frequencies

of the ss phenotype are close to data reported previously in Africans (68%)[26]. In some studies carried out in Africa, the frequencies of the MNSs antigens reveal major differences between ethnicities. This was observed in Tanzania in three ethnic groups who have shown significant differences in the distribution of MNS phenotype[27], in Benin for the Ss phenotype[28], among Africans of Cape in South-Africa[29] and this is also the case for various ethnic groups including Somalia[30]. This system should be studied in a larger sample because this disparity in the distribution of antigens presents a high risk of alloimmunization during transfusions and pregnancy. Of note, the extended phenotype is not carried out in standard pre-transfusion workup in Africa.

DISCUSSION

We note the presence of S-s- phenotype in both populations with frequencies of 1.2% among the Yansi and 3.4% among the control group. The reported frequency of S-s- phenotype in Africans is around 1.5%[26]. There are individuals devoid of the U antigen who do not have both the S and s antigens. The U- phenotype is of low incidence in Africans and is absent in Caucasians[26]. Immunologic challenge of S-s- persons most often stimulates the production of anti-U, which is known to cause decreased survival of transfused antigen-positive red blood cells[26,31].

As for the Kidd system, there was no significant difference (Table 1) with 37.5% of Jk (a+b+) among the Yansi and 30.1% among the control group; 55.1% of Jk (a+b-) among the Yansi and 64.3% of Jk (a+b-) among the control group. Reported distribution in Africans is as follows: 34% for Jk (a+b+), 57% for Jk (a+b-) and 9% for Jk (a-b-)[32].

The distribution of AA and AS hemoglobin did not differ between groups ($P = 0.24$). Among the Yansi population, 78.1% and 21.9% of subjects exhibited AA and AS phenotype, respectively. Among the control group, 82.2% and 17.8% of subjects presented with AA and AS phenotype, respectively (Table 2). It is assumed that SS individuals were not found because of early mortality. In the Democratic Republic of the Congo, the sickle-cell anemia trait has a frequency ranging from 15% to 20%, which is also the case of Central Africa[18,33-35].

As for the G6PD phenotype, there was no significant difference between groups ($P = 0.74$). Among the Yansi, we noted 11.7% of subjects with G6PD deficiency, and among the control group, 12.3% were G6PD deficient (Table 2). Among the control group, the distribution according to sex showed a significant difference ($P = 0.023$): the proportion of males was much higher in the G6PD deficient group compared to the G6PD normal group (Table 3). The high frequency of G6PD deficiency in males is explained by the fact that the coding gene for G6PD is located on the X chromosome, and therefore, the deficiency is fully expressed in the boys affected in the hemizygote manner[36]. The distribution according to sex shows a non-significant difference ($P = 0.83$) in the Yansi: among G6PD deficient subjects, 46.7% were males and 53.3% were females. This may be due to selection of mutant alleles by consanguinity. Indeed, many variants of G6PD deficiency have been described with more than 140 known mutations, with variable enzymatic activity[36,37]. Two possibilities may arise: first, double heterozygous women carrying a completely silent allele and a partially silent allele may present with overall enzyme activity below the test cut-off. In this case they are categorized as deficient and their frequency will increase compared to controls. Second, men with a partially silent allele may be categorized as non deficient if the enzyme activity is above the test cut-off. In this case the frequency of G6PD deficient subjects will decrease compared to controls. On the other side, in normal G6PD subjects of the Yansi population, 44.7% were males and 55.3% were females (Table 3).

We noticed during our survey that several subjects of the population Yansi died prematurely. That can be explained by the presence of congenital defects and/or malformative disorders associated to consanguinity[38,39], which has been reported in several populations[40,41]. Such occurrences generate a bias in the population Yansi as miscarriage and infant mortality are superior in Yansi than within control population (Table 4). However, our data do not provide a causal link between the occurrence of theses disorders and consanguinity. To get more reliable information on the consequences of consanguinity, biological parameters should be tested at birth, through newborn screening. This may help in sensitizing the Congolese population about the medical risks associated

Table 2 Distribution of glucose-6-phosphate dehydrogenase and hemoglobin phenotype in Yansi population and control subjects *n* (%)

	Yansi *n* = 256	Control *n* = 269	*P* value
G6PD			0.74
Normal	226 (88.3)	235 (87.4)	
Deficient	30 (11.7)	34 (12.3)	
Hemoglobin			0.24
AA	200 (78.1)	221 (82.2)	
AS	56 (21.9)	48 (17.8)	

G6PD: Glucose-6-phosphate dehydrogenase deficiency.

Table 3 Distribution of glucose-6-phosphate dehydrogenase deficiency in relation to gender in Yansi population and control subjects *n* (%)

Population	Male	Female	*P* value
Yansi (*n* = 256)			0.83
G6PD normal	101 (44.7)	125 (55.3)	
G6PD deficient	14 (46.7)	16 (53.3)	
Control (*n* = 269)			0.023
G6PD normal	117 (49.8)	118 (50.2)	
G6PD deficient	24 (70.6)	10 (29.4)	

G6PD: Glucose-6-phosphate dehydrogenase deficiency.

Table 4 Clinical disorders observed in the two populations *n* (%)

Clinical disorders	Yansi *n* = 256	Control *n* = 269	*P* value
	M = 115; W = 141	M = 141; W = 128	
Asthma	8 (3.1)	-	-
Rheumatism	20 (7.8)	-	-
Paralysis	2 (0.8)	-	-
Sterility	1 (1.4)	-	-
Sexual impotence	1 (0.4)	-	-
Epilepsy	13 (5.1)	-	-
Deafness	1 (0.4)	-	-
Miscarriage	46 (32.6)[1]	3 (2.3)[1]	< 0.0001
Stilbirth	4 (2.8)[1]	-	-
Death in young age	62 (24.2)	3 (2.3)	< 0.0001

[1]Percentage among women of childbearing age. M: Men; W: Women.

with consanguineous unions and in building up a database of genetic diseases in the population.

In conclusion, we present in this paper an overview of the blood group phenotypes, hemoglobin S and G6PD deficiency among populations for which few studies have been done to date. In view of our results we find that the different studied markers are not affected by consanguinity in general because the frequency of different variables of consanguineous subjects is not statistically different from that of the unrelated subjects. Nevertheless, the fact that level of MNS blood groups presented relevant difference in Yansi, and also the high frequency of clinical disorder show us that consanguinity brings genetic disorders in this population. Screening of a wider cohort could bring more clarification on the effects of consanguinity on the phenotypes under study in the present paper.

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COMMENTS

Background

The frequency of ABO and Rh blood groups, and of the other blood systems such as Kell, Duffy, Kidd and MNS differs between populations. Blood groups antigens are most important in transfusion, pregnancy and transplantation because of their immunogenic capacity. Distribution of blood groups is not known in Yansi tribe practicing consanguineous marriage. Consanguinity increases the risk of developing genetic diseases. Therefore this study also evaluated the frequency of glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency and sickle-cell anemia trait.

Research frontiers

The comparison between consanguineous Yansi and unrelated subject showed relevant difference in distribution of MNS blood groups. Authors also found high frequency of clinical disorders in Yansi population.

Innovations and breakthroughs

It is known that bloods group phenotypes, sickle-cell anemia trait and G6PD deficiency are significant on the medical and anthropological level but also that consanguinity brings genetics disorders in the population. Several studies have been conducted in various African countries but few studies have been done to date in Congolese population in general and in the Yansi tribe in particular. To our knowledge, this study is the first to report data on this specific population.

Applications

This study will contribute to build a database of genetic diseases in the population and it will help in sensitizing the population about the medical risks associated with consanguineous unions.

Peer review

The study aimed to determine the frequency of blood groups antigens in the ABO, Rh and other systems as well as the prevalence of sickle-cell anemia's trait and the G6PD among the consanguineous Yansi tribe in the Democratic Republic of the Congo. The study revealed a significant difference in MNS blood group distribution between the Yansi tribe and a control population. Thus new data has been provided that consanguinity brings genetic disorders in the population. The paper is interesting and timely.

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