


# The Distributions of Duffy Antigens and Phenotypes Among Blood Donors in King Abdulaziz Medical City-Western Region, Saudi Arabia: A Cross-Sectional Study

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**Purpose:** The Duffy (FY) is considered one of the clinically significant blood group systems. Anti-Fy<sup>a</sup> and anti-Fy<sup>b</sup> can cause hemolytic transfusion reactions and hemolytic disease of the fetus and newborn. This study investigated the prevalence of FY antigens and phenotypes in Saudi Arabian and non-Saudi Arabian blood donors.

**Methods:** A total of 25611 blood donors were enrolled in this study from January 2020 to May 2024, at the blood bank center of King Abdulaziz Medical City-Western Region (KAMC-WR), Jeddah, Saudi Arabia. Serotyping was conducted to identify Fy<sup>a</sup> and Fy<sup>b</sup> antigens as well as the four FY phenotypes using a solid phase technique.

**Results:** The majority of the blood donors were Saudi Arabians (n = 21,496, 83.93%), while the remaining donors were non-Saudis (n = 4115, 16.07%). The frequencies of Fy<sup>a</sup> and Fy<sup>b</sup> among the Saudi Arabian donors were 28.20% and 28.41%, respectively. Conversely, the distributions of the Fy<sup>a</sup> and Fy<sup>b</sup> antigens among the non-Saudi Arabian donors occurred at 44.88% and 39.83%, respectively. The Fy(a-b-) phenotype was the most common FY phenotypes among the Saudi Arabian and non-Saudi Arabian and were 50.07% and 33.80%, respectively. The incidences of the FY phenotypes were statistically significantly different in Saudis compared to non-Saudis (p < 0.01).

**Conclusion:** The prevalence of the FY antigens and phenotypes is reported among blood donors. The Fy(a-b-) phenotype was the most widespread among Saudis and non-Saudis. It is crucial to include the FY antigens in the transfusion screening panel especially for both blood donors as well as patients especially the transfusion-dependent patients.

**Keywords:** Duffy blood group, Duffy-null, blood donors, immunohematology, Saudi Arabia

## Introduction

In 1950, Cutbush first reported the Duffy (FY) blood group when he documented the reaction of an antibody identified in a hemophilic male patient who received multiple blood transfusion units. Notably, his plasma displayed an alloantibody against an antigen known as Fy<sup>a</sup>.<sup>1</sup> In the following year, an antibody was identified in the serum of a multiparous female and called anti-Fy<sup>b</sup>, which is an antibody to the antithetical Fy<sup>b</sup> antigen.<sup>2</sup> Nowadays, the FY blood group system is the eighth classification system according to the International Society of Blood Transfusion. The system comprises five antigens, of which Fy<sup>a</sup> and Fy<sup>b</sup> are the main antigens.<sup>3</sup>

The FY system is represented by a single gene, *atypical chemokine receptor 1 (ACKR1)*, formerly known as the *Duffy antigen receptor for chemokines (DARC)* gene. This gene is located on the long arm of chromosome 1q21-22 and consists of two exons.<sup>4</sup> The gene encodes the FY antigens that are located on a glycoprotein that is 336 amino acid residues in length and traverses the red cell membrane several times, forming seven extracellular loops and containing an N-glycosylation site. The N-terminal is extracellular, and the C-terminal is intracellular.<sup>5,6</sup>

The FY alleles include *FY\*A*, *FY\*B*, *FY\*X*, and *FY-nulli*.<sup>7</sup> The *FY\*A* and *FY\*B* alleles are responsible for the Fy<sup>a</sup> and Fy<sup>b</sup> antigens, respectively. A single nucleotide variant (c.125G>A) is the difference between the *FY\*A* and *FY\*B* alleles as it causes an amino acid substitution (Gly42Asp).<sup>8</sup> Four possible phenotypes result from these two antigens: Fy(a<sup>+</sup>b<sup>-</sup>), Fy(a<sup>-</sup>b<sup>+</sup>), Fy(a<sup>+</sup>b<sup>+</sup>), and FY<sub>null</sub> or Fy(a<sup>-</sup>b<sup>-</sup>).<sup>8</sup> The distribution of these phenotypes varies across populations based on their ethnic backgrounds.

The Fy<sup>a</sup> and Fy<sup>b</sup> antigen prevalence in Saudi Arabia is 13–22% and 11–22%, respectively.<sup>9,10</sup> The reported phenotypes were: Fy(a<sup>+</sup>b<sup>-</sup>), 17% in Eastern Province and 10.48% in Jazan Province; Fy(a<sup>-</sup>b<sup>+</sup>), 17% in Eastern Province and 9.10% in Jazan Province; Fy(a<sup>+</sup>b<sup>+</sup>), 5% in Eastern Province and 2.10% in Jazan Province; and FY<sub>null</sub>, 61% in Eastern Province and 78.32% in Jazan Province.<sup>9,10</sup> Therefore, the FY<sub>null</sub> phenotype occurs at high frequencies in Saudi Arabian populations.

Alloimmunization to anti-Fy<sup>a</sup> and anti-Fy<sup>b</sup> antibodies typically occurs after receiving a blood transfusion of FY phenotype-incompatible red cells or, less commonly, after pregnancy due to hemolytic disease of the fetus and newborn (HDFN).<sup>11,12</sup> Anti-Fy<sup>a</sup> may fix the complement, resulting in acute hemolytic transfusion reactions (HTR).<sup>11</sup> Anti-Fy<sup>b</sup> seems incapable of complement fixation and does not result in immediate HTR. However, both can result in delayed HTR.<sup>13–15</sup>

A high incidence of transfusion-dependent patients reside in Saudi Arabia due to the high prevalence of sickle cell disease (SCD) and thalassemia. These individuals require regular blood transfusion units, which may increase the risk of the red cell alloimmunization.<sup>16,17</sup>

Given the importance of the FY blood groups for HTR, this study sought to identify the prevalence of FY antigens and phenotypes among Saudi Arabian and non-Saudi Arabian blood donors in King Abdulaziz Medical City in Jeddah, Saudi Arabia.

## Materials and Methods

### Blood Samples

Ethical approval was obtained from Institutional Review Board at King Abdullah International Medical Research Center (No. 0000086124), Ministry of National Guard Health Affairs, Kingdom of Saudi Arabia. A cross-sectional study was conducted on 25611 blood samples that were obtained from healthy volunteer blood donors, between January 2020 and May 2024, at the blood bank center of King Abdulaziz Medical City-Western Region (KAMC-WR), Jeddah, Saudi Arabia.

Informed consent was given and signed by the blood donors to participate in this study. Their data were secured in a computerized database and handled using only the blood donation numbers to maintain their confidentiality. Therefore, the blood donors cannot be identified, and there are no implications for the donors' health and welfare. This study complies with the Declaration of Helsinki.

Contributors to this study donated blood according to the criteria set by the Saudi Central Board for Accreditation of Healthcare Institutions (CBAHI). The blood units were screened for any infectious diseases for the recipients' safety.

### Immunochemistry

Serotyping was conducted with a solid phase technique using anti-Fy(a) micro and anti-Fy(b) micro antibodies according to the manufacturer's instructions (Immucor Medizinische Diagnostik GmbH, Dreieich, Germany). Positive reactions included agglutination and antibody clumping with the FY antigens, indicating the presence of the antigen, while negative reactions included a lack of agglutination between the antibodies and antigens, indicating the absence of FY antigens for the given sample.

## Statistics

Based on the estimated population of Jeddah City (3.71 million), the required sample size was calculated to a total number of 664 samples. This was conducted with Raosoft Sample Size Calculator with a 99% confidence level and a 5% margin of errors. The distribution of the FY antigens and phenotypes among Saudi and non-Saudi donors was demonstrated and standardized as percentages. The groups were compared with a chi-squared test to identify statistically significant results. *p*-values of <0.01 indicated a highly significant difference.

## Results

A total of 25611 blood donors were enrolled in this study. Table 1 presents the participants' sociodemographic data. Most of the blood donors were Saudi Arabians (n = 21,496, 83.93%). The remaining donors were non-Saudi Arabians (n = 4115, 16.07%).

The incidences of the Fy<sup>a</sup> and Fy<sup>b</sup> antigens are presented in Table 2. The Saudi Arabians expressed lower frequencies of the Fy<sup>a</sup> and Fy<sup>b</sup> antigens compared to non-Saudi Arabians, which were 28.20% and 28.41%, respectively. On the other hand, the distributions of Fy<sup>a</sup> and Fy<sup>b</sup> antigens in non-Saudi Arabians were 44.88% and 39.83%, respectively.

Table 3 shows the different FY phenotypes among the two groups. The most common phenotype was the FY<sub>null</sub>, ie, Fy(a<sup>-</sup>b<sup>-</sup>). Interestingly, the Fy(a<sup>-</sup>b<sup>-</sup>) phenotype was observed in high frequencies in Saudi Arabians (50.07%) compared

**Table 1** Sociodemographic Data of the Blood Donors in the Present Study (n = 25,611)

Nationality	n	%
Saudi	21496	83.93
Non-Saudi	4115	16.07
Total	25611	100

**Table 2** Comparison of Prevalence of FY Antigens Between Saudi Arabians and Non-Saudi Arabians

Antigen	Saudi Arabians (n = 21496)		Non-Saudi Arabians (n = 4115)		Chi square	P-value
	Observation	Frequency (%)	Observation	Frequency (%)		
Fy <sup>a</sup>	6062	28.20	1847	44.88	10.88	0.0009 <sup>§</sup>
Fy <sup>b</sup>	6107	28.41	1639	39.83		

Note: FY = Duffy, <sup>§</sup>Highly significant (P<0.01).

**Table 3** Comparison of Distribution of FY Phenotypes Between Saudi Arabian Population versus Non-Saudi Arabians

Phenotype	Saudi Arabians (n = 21496)		Non-Saudi Arabians (n = 4115)		Chi square	p-value
	Observation	Frequency (%)	Observation	Frequency (%)		
Fy(a <sup>-</sup> b <sup>-</sup> )	4628	21.53	1085	26.37	795.71	0.0001 <sup>§</sup>
Fy(a <sup>+</sup> b <sup>+</sup> )	1432	6.66	762	18.52		
Fy(a <sup>-</sup> b <sup>+</sup> )	4674	21.74	877	21.31		
Fy(a <sup>+</sup> b <sup>-</sup> )	10,762	50.07	1391	33.80		
	21,496	100	4115	100		

Note: FY = Duffy, <sup>§</sup>Highly significant (P<0.01).

**Table 4** FY Phenotype Frequencies in the Saudi Population in the Current Study Compared to Different Regions in Saudi Arabia

Phenotype	Current (%) n = 21496	Jazan <sup>9</sup> (%) n = 143	Eastern <sup>10</sup> (%) n = 100	Al-Ahsa <sup>18</sup> (%) n = 1549	Turaba <sup>19</sup> (%) n = 400
Fy(a+b <sup>-</sup> )	21.53	10.48	17	10.2	28
Fy(a+b <sup>+</sup> )	6.66	2.10	5	4.1	38
Fy(a <sup>-</sup> b <sup>+</sup> )	21.74	9.10*	17	11.5	16
Fy(a <sup>-</sup> b <sup>-</sup> )	50.07	78.32	61	74.1	18
P-values		Current/Jazan P = 0.0005 <sup>§</sup>	Current/Eastern P = 0.48	Current/Al-Ahsa P = 0.0059 <sup>§</sup>	Current/Turaba P = 0.0002 <sup>§</sup>

**Note:** FY = Duffy, <sup>§</sup>Highly significant (P<0.01).

to non-Saudi Arabians (33.80%). The difference in FY phenotypes among Saudi Arabians from different regions were compared as illustrated in Table 4. The Fy<sub>null</sub> phenotype was the most prevalent among Saudi Arabians in various regions, including Jazan, Al-Ahsa and Eastern Province.<sup>9,10,18</sup> However, in Turaba Province, only 18% of Saudi Arabians exhibited the Fy<sub>null</sub> phenotype, with Fy(a<sup>+</sup>b<sup>+</sup>) being the most common FY phenotype.<sup>19</sup>

## Discussion

Understanding the frequencies of various blood group antigens is essential to avoid HTR. This is because many transfusion-dependent patients in Saudi Arabia may require regular blood transfusions, especially those suffering from sickle cell disease and thalassemia.<sup>20,21</sup> Because such patients receive multiple blood units by transfusion, their risk of red cell alloimmunization is elevated.<sup>22</sup> Therefore, many studies have been conducted regarding the prevalence of various blood groups in Saudi Arabia.<sup>23–33</sup>

In this study, two main antigens of the FY blood group system were assessed in KAMC-WR (Jeddah City, Saudi Arabia) as well as their four possible phenotypes, for both Saudi Arabian and non-Saudi Arabian blood donors. The frequencies of the Fy<sup>a</sup> and Fy<sup>b</sup> antigens among Saudis in the current study were 28.20% and 28.41%, respectively. On the other hand, the rates of Fy<sup>a</sup> and Fy<sup>b</sup> antigens in the non-Saudi blood donors were higher than those in the Saudi blood donors, which were 44.88% and 39.83%, respectively.

The frequency of the Fy<sup>a</sup> antigen varies as follows: 66% in Caucasian people, 10% in Black people, 99% in Asian people, and 97% in Thai people. Meanwhile, the frequency of the Fy<sup>b</sup> antigen is 83% in Caucasian people, 23% in Black people, 18.5% in Asian people, and 31% in Thai people.<sup>34</sup>

Regarding the phenotypes, the Fy(a<sup>+</sup>b<sup>-</sup>) phenotype is common in the Asian population, while the Fy(a<sup>-</sup>b<sup>+</sup>) phenotype is more common in Caucasian people. The most common phenotype in Black individuals was the Fy<sub>null</sub> phenotype at 68%.<sup>34</sup>

This study demonstrated a statistically significant difference ( $P < 0.01$ ) in FY phenotypes between the Saudi blood donors and the non-Saudis, as Table 3 shows. The prevalences of the Fy(a<sup>+</sup>b<sup>-</sup>) and Fy(a<sup>-</sup>b<sup>+</sup>) phenotypes in Saudi Arabians were 21.53% and 21.74%, respectively. The prevalence of the Fy(a<sup>+</sup>b<sup>-</sup>) phenotype in Saudi Arabians was significantly lower than that reported in the Chinese population (89.2%).<sup>35</sup> The most frequent FY phenotype was the null phenotype, Fy(a<sup>-</sup>b<sup>-</sup>), in both populations.

Interestingly, the prevalence of the Fy(a<sup>-</sup>b<sup>-</sup>) phenotype in Saudis was 50.07%, which was higher than in non-Saudis (33.80%). In addition, higher observations of the Fy(a<sup>-</sup>b<sup>-</sup>) phenotype were observed among Saudi Arabians living in Eastern Province (61%), Al-Ahsa Province (74.1%), and Jazan Province (78.32%).<sup>9,10,18</sup> On the other hand, an interesting observation has been reported in Turaba Province, Saudi Arabia, where the Fy(a<sup>-</sup>b<sup>-</sup>) phenotype accounts for 18%.<sup>19</sup> This study demonstrated a statistically significant difference ( $P < 0.01$ ) in FY phenotypes between the Saudi blood donors in KAMC-WR in Jeddah City and Saudi Arabians living in Jazan, Al-Ahsa, and Turaba Provinces as demonstrated in Table 4.<sup>9,18,19</sup>

All findings regarding the FY<sub>null</sub> phenotype in Saudi Arabia vary from the reported prevalence in 30 sub-Saharan African countries, which exceeds 90%.<sup>36</sup> These variations may be attributed to the distinct molecular background of the Saudi Arabian population, which differs from other ethnic backgrounds. Serotyping studies of the FY blood group system are recommended among Arab populations and different regions in Saudi Arabia to investigate the prevalence of FY antigens and phenotypes.

This FY<sub>null</sub> phenotype may have a selective benefit of getting infections by *Plasmodium Vivax* and *Plasmodium Knowlesi*.<sup>37</sup> However, a study by Wilairatana et al (2022) showed that *Plasmodium Vivax* can infect the FY<sub>null</sub> individuals.<sup>38</sup>

The recommendation for the transfusion practice in Saudi Arabia to screen for the FY antigens for both blood donors and recipients, Saudis and non-Saudis, especially for the transfusion-dependent patients to preclude the risk of alloimmunization to FY red cell antigens.

The limitations of the present study include the absence of some sociodemographic information, including age and gender, in the retrieved system data is a limitation.

## Conclusion

In conclusion, the prevalence of FY blood group antigens and phenotypes was determined in Saudi Arabian and non-Saudi Arabian blood donors at KAMC-WR in Jeddah City, Saudi Arabia. Interestingly, the most common phenotype among the Saudi Arabian and non-Saudi Arabian populations was Fy(a<sup>-</sup>b<sup>-</sup>). It is highly recommended to include the FY antigens in the transfusion screening panel especially for the transfusion-dependent patients including sickle cell disease and thalassemia patients. Further studies in different parts of Saudi Arabia are highly recommended to investigate the prevalence of various FY antigens and phenotypes.

## Data Sharing Statement

Data available.

## Ethics Approval and Informed Consent

Ethical approval was obtained from Institutional Review Board at King Abdullah International Medical Research Center (No. 0000086124), Ministry of National Guard Health Affairs, Kingdom of Saudi Arabia.

The study was conducted in accordance with the Declaration of Helsinki. Informed consent of the blood donors was waived by the IRB because of the retrospective nature of the research, which focused on reviewing the blood donors' medical records.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no conflict of interest.

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