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ORIGINAL RESEARCH

The Incidences of KEL Blood Group Antigens and Phenotypes in Southwestern Saudi Arabia

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Purpose: Jazan Province in Saudi Arabia is notable for its high prevalence of inherited hemoglobinopathies, including sickle cell disease and thalassemia, necessitating frequent blood transfusions for affected individuals. To mitigate risks such as RBC alloimmunization and hemolytic transfusion reactions, ensuring blood compatibility is crucial. The Kell (KEL) blood group system, pivotal alongside the ABO and RH systems, encompasses multiple antigens implicated in these complications. This study aimed to investigate the frequencies of KEL blood group antigens (K, k, Kpa, and Kpb) and determine KEL phenotypes (K/k and Kpa/Kpb) among Saudi blood donors living in Jazan Province.

Methods: A total of 138 anonymous healthy Saudi blood donors from Prince Mohammed bin Nasser Hospital in Jazan Province, Saudi Arabia, were enrolled in this study. Anticoagulated blood was analyzed using the gel card technique to assess K, k, Kpa, and Kpb antigens.

Results: The prevalence of KEL antigens was as follows: K (n = 9, 6.52%), k (n = 137, 99.28%), Kpa (n = 1, 0.72%), and Kpb (n = 138, 100%). KEL phenotypes observed were K+k+ (n = 8, 5.80%), K+k− (n = 1 0.72%), K−k+ (n = 129, 93.48%), Kp(a+b+) (n = 1, 0.72%), and Kp(a−b+) (n = 137, 99.28%).

Conclusion: This study provides insights into the prevalence of KEL blood group antigens and phenotypes in Jazan Province, Saudi Arabia. These findings may contribute to the establishment of a national blood group database and guide transfusion practices to ensure compatibility and minimize alloimmunization risks.

Keywords: Kell blood group, blood transfusion, immunohematology, Saudi Arabia

Introduction

The Kell (KEL) blood group is named after the first antibody producer of the system, "Mrs. Kelleher", who developed an anti-K antibody after giving birth to a stillborn baby. This condition is now known as hemolytic disease of fetus and newborn (HDFN).[1] The KEL blood group system is considered to be the most important blood group system after the ABO and RH systems and is ranked as the sixth system among all blood groups by the International Society of Blood Transfusion (ISBT).[2]

Several molecular studies have defined the *KEL* gene and the primary structure of its protein. The sequence analysis shows that the human *KEL* is located on chromosome 7q33 and contains 19 exons spanning about 21.5 Kbp. The gene exhibits a high level of polymorphism, resulting in point mutations and amino acid substitutions.[3,4]

The KEL protein is a type II single-pass transmembrane glycoprotein with a molecular mass of 93 kDa. The N-terminal of the protein is located in the cytoplasmic region and consists of 47 amino acids, while the C-terminal is

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in the extracellular region and contains 665 amino acids.[5] Molecular studies indicate that the KEL glycoprotein shares sequence homology with the neutral zinc-endopeptidase and acts as a proteolytic enzyme and a potent bioactive peptide.[6] The KEL glycoprotein is widely distributed in various body tissues and not restricted to erythroid cells.[7,8]

The KEL blood group system includes 38 antigens, categorized into low and high frequencies. Some of these are antithetical antigens, which express eight sets of 17 antithetical antigens and 12 low prevalent antigens. The most important antigens in the KEL system are K, k, Kpa, Kpb, Jsa, and Jsb.[2]

The anti-K is the most immunogenic antibody in the KEL system. It is an IgG antibody capable of causing extravascular hemolysis, leading to severe complications such as HDFN and hemolytic transfusion reactions (HTR).[9]

A high incidence of red cell alloimmunization is observed during pregnancy due to K antigen incompatibility between fetal red blood cells (RBCs; K+) and the mother (K−). Consequently, the mother's immune system recognizes the fetal RBCs as foreign and produces anti-K antibodies.[10] Interestingly, Bahkali et al reported a case in Saudi Arabia of a pregnant woman that was alloimmunized and produced anti-K during her third pregnancy, leading to a dead baby after two months of delivery.[11]

The risk of experiencing HDFN is heightened in women who have undergone multiple blood transfusions and developed antibodies against the K antigen. Unlike ABO and RH antigens, KEL antigens are expressed earlier on the surface of RBC precursors. The severity of HDFN does not correlate with antibody titers or bilirubin levels in the amniotic fluid but rather mimics the inhibition of fetal erythropoiesis.[12]

HTR can occur when incompatible blood is transfused into a recipient. These reactions are caused by antibodies such as anti-K, anti-k, anti-Kpa, and anti-Jsb, which are present in the recipient's blood and react with antigens on the transfused RBCs, leading to the destruction of donor RBCs[13] Therefore, it is crucial to investigate the frequencies of KEL antigens in populations to avoid RBC alloimmunization.

The distribution of K and k antigens exhibits significant regional variations globally. In Mainland China, the frequency of the K antigen is approximately 0.14%, while the prevalence of the k antigen is 100%.[14] However, in India, only 5.56% of individuals are positive for the K antigen, while 100% are positive for the k antigen.[15] The frequencies of the K and k antigens in Blacks were reported at 2% and 100%, respectively. On the other hand, the Caucasians observed 9% for the K antigen and 99.8% for the k antigen.[16] These findings highlight the differences in antigen prevalence between these populations.

Several studies on the prevalence of the KEL blood group system have been conducted in the Eastern and Western provinces of Saudi Arabia. The occurrence of the K antigen ranges from 8−18.2%, while the prevalence of the k antigen ranges from 98−100%. The Kpa antigen is observed at a frequency of 4%, while the Kpb antigen ranges from 96% to 100%.[17–19]

In Jazan Province, located in the southwestern region of Saudi Arabia, the prevalence of KEL antigens has not yet been investigated. The region is endemic for hemoglobinopathies requiring multiple transfusion units such as sickle cell disease (SCD) and thalassemia.[20] Appropriate matching for KEL antigens is essential to reduce the incidence of RBC alloimmunization.[21] Halawani et al (2021) reported the alloimmunization by the anti-K and anti-Kpa in the SCD and thalassemia patients were 14.06% and 3.13%, respectively.

Given the importance of KEL blood group antigens in HTR and HDFN, this project aims to determine the prevalence of KEL blood group antigens (K, k, Kpa, Kpb) and KEL phenotypes among Saudi blood donors in Jazan Province, Saudi Arabia.

Materials and Methods

Participant Selection and Blood Sampling

A total of 138 anonymous voluntary Saudi citizen regular blood donors residing in the Jazan Province of Saudi Arabia were enrolled in this study. Blood was collected in ethylenediamine tetraacetate (EDTA) tubes. The study was approved by the Jazan Health Ethics Committee (H-10-Z-073, No. 2386). Participants donated blood voluntarily at the blood bank in Prince Mohammed bin Nasser Hospital (PMBNH) after signing an informed consent form, agreeing to participate in the study, and completing a donation questionnaire.

Inclusion Criteria

Participants were regular voluntary Saudi Arabian citizens residing in Jazan Province who met the donor eligibility criteria of the National Standards for Clinical Laboratories and Blood Banks, defined by the Saudi Central Board for Accreditation of Healthcare Institutions (CBAHI).

The transfusion eligibility criteria included patients aged 17−65 years old, a minimum weight of 55 kg, a body temperature not exceeding 37.5 °C, and the hemoglobin level should be more than 12.5 g/dL. Additionally, participants were required to have no history of liver diseases, cancer, or bleeding tendencies, or travel history to regions of endemicity for malaria, human immunodeficiency virus (HIV), or variant Creutzfeldt-Jakob disease. Furthermore, blood donors were screened to ensure they were negative for transfusion-transmitted diseases, including hepatitis B virus (HBV), hepatitis C virus (HCV), malaria, HIV 1 and 2, human T-lymphotropic virus 1 and 2, and syphilis.

Exclusion Criteria

Non-Saudi Arabian blood donors and Saudi Arabians from provinces other than Jazan were excluded from this study. In addition, any blood samples that tested positive for the infectious diseases listed above were excluded.

Immunohematology Assessment

Serotyping was performed on the study population using commercial kits based on gel card technology. The DiaClon Rh-Subgroups + K kit was used to type the K antigen, and the Antigen Profile-II kit was used to type the k, Kpa, and Kpb antigens using the IH-1000 automated system following the manufacturer's instructions (Diamed GmbH, Cressier, Switzerland).

A pellet at the bottom of the microtubes resulting from the reaction indicated a negative result and the absence of the antigen of interest. Conversely, a positive result, indicated by a distinct red line or cell diffusion, was classified as 1+, 2+, 3+, or 4+ based on the strength of the reaction, signifying the presence of the corresponding antigen.

Statistical Analysis

The sample size was calculated using Raosoft Sample Size Calculator. The sample size was estimated to 119 samples with a 95% confidence level and a 9% margin of error. The prevalence of K, k, Kpa, and Kpb antigens, as well as the KEL phenotypes, is expressed as percentages. A chi-squared test was conducted using SPSS software Version 28 (SPSS, Inc., Chicago, United States). The p-values of <0.05 and <0.01 indicating significant and highly significant differences, respectively.

Results

In this study, 138 Saudi blood donors from the Jazan Province of Saudi Arabia. Unexpectedly, all the participants were males (100%, n = 138). They were screened for the following antigens: K, k, Kpa, and Kpb. The frequencies of these antigens are displayed in Table 1. The K and k antigens were found at frequencies of 6.52% (n = 9) and 99.28% (n = 137), respectively. The Kpb antigen was the most common, present in all participant samples (100%, n = 138), while the Kpa antigen was the least common (0.72%, n = 1), observed in only one sample.

The KEL phenotypes of the Jazan population are presented in Table 2. The most frequently detected phenotype was K−k+ at 93.48%. Interestingly, the homozygous phenotype for the K antigen, K+k−, was observed in 0.72% of the samples, while the heterozygous phenotype, K+k+, was found in 5.8% of the samples. The Kp(a−b+) phenotype was the most common among the KEL phenotypes, accounting for 99.28% of the samples. Notably, the Kp(a+b+) phenotype was observed in 0.72% of the samples. Tables 3 and 4 compare the KEL antigens and phenotypes of the current study to those from different ethnic backgrounds.

Discussion

The Jazan Province of Saudi Arabia is highly endemic for inherited hemoglobinopathies such as SCD and thalassemia.[26] Affected patients may require frequent blood transfusions. This increases the risk of RBC alloimmunization due to

Table 1 Frequencies of KEL Antigens Among Saudi Arabians in Jazan Province

Antigen	n	%
K	9	6.52
k	137	99.28
Kpa	1	0.72
Kpb	138	100

Table 2 Frequencies of KEL Phenotypes Among Saudi Arabians in Jazan Province

Phenotype	n	%
K+k+	8	5.8
K+k−	1	0.72
K−k+	129	93.48
Kp(a+b+)	1	0.72
Kp(a−b+)	137	99.28

Table 3 Comparison of KEL Antigen Prevalence Between the Current Study and Similar Studies Conducted in Saudi Arabia and Worldwide

Antigen	Current study (%)	Jeddah, Saudi Arabia[17]	Riyadh, Saudi Arabia[19]	Oman[22]	Han descent, Mainland China[23]	India[15]	Morocco[24]	Iran[25]
K	6.52	16.3	18.2	4.5	0.14	5.56	0.19	8
k	99.28	98.5	97.0	99.4	100	100	99.80	97.7
Kpa	0.72	4.0	11.7	2.7	0.28	0.95	0	9.3
Kpb	100	100	96.0	100	100	100	0	96.7
p-values		Jazan /Jeddah p = 0.105	Jazan /Riyadh p = 0.002**	Jazan /Oman p = 0.678	Jazan /China p = 0.101	Jazan /India p = 0.99	Jazan /Morocco p = 0**	Jazan /Iran p = 0.05*

Notes: *significant, **Highly significant.

mismatching of the blood group antigens.[21] Therefore, understanding the frequencies and the extended matching of blood group antigens may mitigate this risk, as highlighted in our previous research.[27–33]

Normally, in PMBNH, routine testing for both blood donors as well as the recipients, including the SCD and thalassemia patients, is to type the ABO, D, C, c, E, e and K antigens. In case of the transfusion-dependent patients observe an unprecedented antibody on the antibody screening, matched blood units will be provided to such patients. In this study, we reported the prevalence of 6.52% of the K antigen among Saudi Arabians living in Jazan Province. Comparable frequencies have been reported in India (5.56%) and Oman (4.5%). In contrast, a higher frequency of 18.2% has been documented in Riyadh City in Saudi Arabia.[15,17,22] Remarkably low prevalences of the K antigen have been

Table 4 Comparison of KEL Phenotype Prevalence Between the Current Study and Similar Studies Conducted in Saudi Arabia and Worldwide

Studies/ Phenotypes	Current study (%)	Jeddah, Saudi Arabia[17]	Riyadh, Saudi Arabia[19]	Oman[22]	Han descent, Mainland China[23]	India[15]	Morocco[24]	Iran[25]
K+k+	5.8	14.8	15.5	4.5	0.142	5.68	9.16	5.7
K+k−	0.72	1.5	3	0	0	0	0.19	2.3
K−k+	93.48	83.7	81.5	94.9	99.86	94.32	90.64	92.0
K−k−	0	0	0	0.6	–	–	–	–
Kp(a+b+)	0.72	4.0	7.8	2.7	0.28	0.95	0	6.0
Kp(a−b+)	99.28	96.0	88.0	97.3	99.72	99.05	0	90.7
p-values		Jazan /Jeddah p = 0.131	Jazan /Riyadh p = 0.01*	Jazan /Oman p = 0.5	Jazan /China p = 0.163	Jazan /India p = 0.944	Jazan /Morocco p = 0*	Jazan /Iran p = 0.253

Notes: *Highly significant.

identified in China (0.14%) and Morocco (0.19%).[23,24] In Jazan Province, we identified the k antigen in 99.28% of the study population, consistent with findings reported in other studies (Table 3).

In our study, the occurrence of the Kpa and Kpb antigens was 0.72% and 100%, respectively. Low prevalences of the Kpa antigen were reported in India (0.95%) and among individuals of Han descent in Mainland China (0.28%).[15,23] However, higher incidences were observed in Riyadh City (11.7%) and Iran (9.3%).[19,25] Statistically significant differences in KEL antigens were observed between the Saudi Arabian population in Jazan Province compared to Riyadh City ($p < 0.01$),[19] Morocco ($p < 0.01$),[24] and Iran ($p < 0.05$),[25] as demonstrated in Table 3. It is highly recommended to include the K and Kpa antigens in the screening panel for both donors and patients to increase compatibility and preclude red cell alloimmunization.[19]

Regarding the KEL phenotype, the prevalence of the K+k+ phenotype in Jazan Province was 5.8%. This closely mirrors findings from India and Iran, which indicated prevalences of 5.68% and 5.7%, respectively.[15,25] However, higher frequencies of this phenotype were reported in Riyadh City (15.5%)[19] and Jeddah City (14.8%)[17] in Saudi Arabia.

The K−k+ phenotype is predominant in the Jazan population at 93.48%. Similar frequencies were observed in Oman (94.9%),[22] India (94.32%),[15] and Iran (92%).[25] Conversely, lower frequencies were reported in Riyadh City[19] and Jeddah City,[17] at 81.5% and 83.7%, respectively.

In this study, the Kp(a+b+) and Kp(a−b+) phenotypes were observed at 0.72% and 99.28%, respectively. Comparable findings were reported in India, where these phenotypes were found at 0.95% and 99.05%, respectively.[15] Conversely, the population studied in Riyadh exhibited different frequencies, with 7.8% for Kp(a+b+) and 88% for Kp(a−b+), as reported in another study.[19] Statistically significant differences in KEL phenotypes were noted between our study and studies conducted in Riyadh[19] ($p < 0.01$) and Morocco[24] ($p < 0.01$), as shown in Table 4.

Conclusion

In summary, this study determined the prevalence of KEL antigens and phenotypes in the Saudi Arabian population residing in Jazan Province. The most prevalent antigens were k and Kpb, while the most common phenotypes were K−k+, and Kp(a−b+). It is highly recommended to include the K and Kpa antigens in the screening panel to preclude red cell alloimmunization. The KEL blood group system plays a vital role in blood transfusion practices due to its clinical significance and is essential in pre-transfusion testing.

Data Sharing Statement

Data available.

Ethics Approval and Informed Consent

Ethical approval was obtained from the Institutional Review Board (IRB) of Jazan Health Ethics, Ministry of Health, Kingdom of Saudi Arabia (No. 2386). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

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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