Kell Blood Group System: A Systematic Review and Meta-Analysis

Tasleem Kausar (tasleem.kausar@gscwu.edu.pk)
Government Sadiq College Women University

Maham Fatima
Government Sadiq College Women University

Shumaila Noureen
Government Sadiq College Women University

Shumaila Javed
Government Sadiq College Women University

Sana Abdulsattar
Government Sadiq College Women University

Fareeha Shahid
Government Sadiq College Women University

Umme Abiha
Government Sadiq College Women University

Rubina Shakeel
Government Sadiq College Women University

Nadia Noureen
Government Sadiq College Women University

Uzma Maqbool
Government Sadiq College Women University

Nabeela Tariq
Sardar Bahadur Khan Women University

Rehan Sadiq
University of the Punjab

Amjad Islam
Cholistan University of Veterinary & Animal Sciences

Research Article

Keywords: Antigen, Epidemiology, Incidence, Kell, Prevalence

Posted Date: October 10th, 2022
Abstract

Background

Kell is highly immunogenic after ABO and Rh blood group system, and anti-Kell antibodies have been linked to hemolytic transfusion reaction and fetal hemolytic disease in newborns. The antithetic KEL1/KEL2, KEL3/KEL4, and KEL6/KEL7 antigens are expressed in the Kell blood group system. At least 36 antigens are carried on a single 93 kDa red-cell trans-membrane protein in the Kell blood system. This study aimed to review different literature on the kell blood group and associated phenotypes and to find out the epidemiology and frequency of different Kell antigens all over the world.

Methods

Epidemiological studies of Kell antigens (2000 to 2022) were extracted to capture all reported data of different kell genotypes/phenotypes from different populations. Different databases like Google Scholar, PubMed, JSTOR, Scopus, and Science Direct were accessed to download all the published data reporting different percentages of kell antigens.

Results

A total of 250 research papers and articles were downloaded; 60 studies met our inclusion criteria. Most of the research studies consisted of KEL1/KEL2, KEL3/ KEL4, and KEL6/KEL7. According to this meta-analysis, the prevalence of KEL1 and KEL3 are lower than KEL2 (100%) and KEL4 (100%). In all captured studies the prevalence of KEL1 ranged from 0 to 23.6%, KEL2 from 0 to 100%, KEL3 from 0 to 11.7%, KEL4 100%, KEL5 0%, KEL6 100%, and KEL7 was 97.31%.

Discussion

This is the first meta-analysis to check the occurrence of Kell blood antigens frequency and the spectrum of variants associated with it in populations of the world. This review will help to identify which is the common antigen of the Kell blood group system and how it can affect the person by disease associated with it.

Introduction

The antigens present in human red blood cells are a collection of glycoproteins and glycolipids. These antigens are genetically regulated, appearing early in fetal life and remain unaltered until death. The most important blood group antigen after ABO, and Rh is the Kell blood group described in different ethnic groups [1]. Coomb, Race, and Mourant discovered the Kell blood group system from a child of Mrs. Kellacher who had the hemolytic disease in a newborn, and the search for antigen led to the finding of a
new antigen, which was dubbed "Kell" [2]. This blood group is ranked the third number of all blood group systems discovered yet, owing to its involvement in immunological reactions. It consists of a single 93 kDa red-cell transmembrane protein that usually carries 36 antigens [3].

The Kell protein consists of 732AA that are glycosylated at five different locations and pass through the membrane of RBC. This protein is associated with another transmembrane protein XK, which anchors it to the RBC surface by a disulfide linkage. McLeod's syndrome develops due to the absence of XK protein. XK protein is a zinc-dependent endopeptidase that cut proteins within the peptide chain and shares sequence and structural similarities with the Kell protein. For catalysis and zinc-binding a pentameric region is required that is found in this protein and other members of this family [4].

The gene of this protein is found at chromosome 7q33 and have 19 exons encompassing more than 20kb of genomic DNA [5]. The SNP (C578T) in exon 6 induces alteration from Threonine to Methionine at 193 positions, resulting in the KEL1 and KEL2 antigens (in the K antigen). A mutation (C841T) in exon 8 resulted in an R281W alteration in KEL3 and KEL4 antigens. A single nucleotide polymorphism (T1790C) in KEL6 which code for proline at position 597, may result in KEL7 antigens, where it codes for leucine (Fig.1), [6].

The common genotypes of Kell blood group system are K+k+, K+k−, K−k+, Kp (a−b+), Kp (a+b+), Kp (a+b−), Js (a−b+), Js (a+b−), Js (a+b−). Out of these, K−k+, Kp (a−b+) and Js (a+b−) have high incidence ratio while K+k+, K+k, Kp (a+b+), Kp (a+b−), Js (a+b+), and Js (a+b−) are low frequency genotypes (Table: 1), [7].

Kell Antigens

In this blood system, 27 antigens are present although only Kell (K1) and cellano (K2) are clinically important. After ABO and Rh antigens, they may be immunogenic since they have been linked to severe hemolytic disease in newborns [8]. Kell antigens are grouped in antipodal set pairings with some antigens that have yet to find antithetical partners [9]. KEL1 (K, "Kell") and KEL2 (k, "Cellano"); KEL3 (Kpa), KEL4 (Kpb), and KEL21 (Kpc); KEL6 (Jsa) and KEL7 (Jsb) are antithetical antigens [10]. KEL4 in contrast to other common antigens is linked to two antithetical antigens KEL3 and KEL21 [9]. Individuals with negative KEL2, KEL4, or KEL7 antigens have uncommon phenotypes, Ko (null) phenotype is present in individuals in which all Kell antigens are absent [11]. The table 1 below expresses the total antigens, their names, notation, and their antigenic frequency.

Table 1: Antigens in KELL Blood Group
<table>
<thead>
<tr>
<th>ISBT No.</th>
<th>Notation</th>
<th>Names</th>
<th>Exon</th>
<th>AA* Change</th>
<th>Frequency</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEL1</td>
<td>K</td>
<td>Kell</td>
<td>6</td>
<td>T 193 M</td>
<td>~2 - 25%</td>
<td>[12]</td>
</tr>
<tr>
<td>KEL2</td>
<td>K</td>
<td>Cellano</td>
<td>11</td>
<td>A 423 V</td>
<td>~100%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL3</td>
<td>Kp&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Penny</td>
<td>8</td>
<td>Arg 281 Trp</td>
<td>~1.99%</td>
<td>[14]</td>
</tr>
<tr>
<td>KEL4</td>
<td>Kp&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rautenberg</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL5</td>
<td>Ku</td>
<td>(K&lt;sub&gt;0&lt;/sub&gt;)</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL6</td>
<td>Js&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sutter</td>
<td>17</td>
<td>Leu 597 Pro</td>
<td>~0.01%</td>
<td>[16]</td>
</tr>
<tr>
<td>KEL7</td>
<td>Js&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Mettheew</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL8</td>
<td>Kw</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>~5%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL9</td>
<td>KL</td>
<td>Claas</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL10</td>
<td>U1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Karhula</td>
<td>13</td>
<td>Glu 494 Val</td>
<td>~2%</td>
<td>[14]</td>
</tr>
<tr>
<td>KEL11</td>
<td>-</td>
<td>Côté</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL12</td>
<td>-</td>
<td>Bockman</td>
<td>15</td>
<td>His 548 Arg</td>
<td>~100%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL13</td>
<td>-</td>
<td>Sgro</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL14</td>
<td>-</td>
<td>Santini</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL15</td>
<td>Kx</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL17</td>
<td>Wk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Weeks</td>
<td>8</td>
<td>Val 302 Ala</td>
<td>~0.3%</td>
<td>[14]</td>
</tr>
<tr>
<td>KEL18</td>
<td>-</td>
<td>Marshall</td>
<td>4</td>
<td>Arg 130 Trp</td>
<td>~100%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL19</td>
<td>-</td>
<td>Sublet</td>
<td>13</td>
<td>Arg 492 Gln</td>
<td>~100%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL20</td>
<td>Km</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL21</td>
<td>Kp&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Leves</td>
<td>8</td>
<td>Arg 281 Gln</td>
<td>~0.01%</td>
<td>[14]</td>
</tr>
<tr>
<td>KEL22</td>
<td>-</td>
<td>Ikar</td>
<td>9</td>
<td>Ala 322 Val</td>
<td>&gt;99.9%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL23</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>Gln 382 Arg</td>
<td>~0.01%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL24</td>
<td>-</td>
<td>Clas</td>
<td>6</td>
<td>Arg 180 Pro</td>
<td>&lt; 0.2%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL25</td>
<td>-</td>
<td>VLAN</td>
<td>-</td>
<td>-</td>
<td>Rare</td>
<td>[15]</td>
</tr>
<tr>
<td>KEL26</td>
<td>-</td>
<td>TOU</td>
<td>11</td>
<td>Arg 406 Gln</td>
<td>~100%</td>
<td>[13]</td>
</tr>
<tr>
<td>KEL27</td>
<td>-</td>
<td>RAZ</td>
<td>-</td>
<td>-</td>
<td>~100%</td>
<td>[15]</td>
</tr>
</tbody>
</table>
*AA stands for Amino acids

**Kell Antibodies and Transfusion Reaction**

Antibodies that target Kell antigens are commonly IgG that are anti-K1, anti-K2, anti-K3, and anti-K7 that become the cause of hemolytic disease in newborns and transfusion reaction [4]. The K1 antibody (anti-K1) is responsible for severe anemia in 10% of cases [17]. The lesser number of cases are caused by anti-K2 [18], anti-K3 [19], anti-K6 [20], and anti-K7 [21] which have been associated with HDFN. Literature reports of the frequency of hemolytic transfusion reactions and the resulting mortality rate of 1/76,000 have been observed [18, 22].

**Common Phenotypes Associated with Kell**

1. **Hemolytic Transfusion Reaction**

The hemolytic transfusion reaction is caused by alloimmunization after transplantation and packed red blood cells (RBCs) transfusions [23]. Transfusion reasons may be mild to severe. These reactions may occur immediately after blood transfusion known as acute transfusion or maybe later after many weeks known as delayed transfusion [24]. The Anti-K, anti-Kp\(^a\), anti-k, and Anti-Js\(^1\) antibodies are responsible for producing a more lethal transfusion reaction [4]. In people with the K\(_0\) phenotype, the production of Ku antibodies led to a lethal transfusion reaction [25].

2. **Hemolytic Disease of Fetus and Newborns**

Antibodies formed as a result of Kell antigen can trigger transfusion reactions and neonatal hemolytic illness (HDN). It usually affects women who have had multiple blood transfusions, but it can also affect moms who had sensitization to Kell antigen in early gestation. Kell sensitization, unlike Rh and ABO hypersensitivity, is produced by anti-K antibodies limiting RBC synthesis in the fetus. Kell antigens are present in the peripheral area of RBC precursors by the tenth week of life, and Kell antibodies promote the macrophages that cause immune destruction of progenitor cells in the liver of the fetus. Since RBC precursors are devoid of Hb, a small quantity of bilirubin is mixed in amniotic fluid during the hemolysis, and anti-Kell antibodies cause fetal anemia by destroying fetal erythroid progenitors [26, 27].

Erythropoiesis is the development of mature red blood cells from erythroid progenitor cells [28]. During early erythropoiesis, the expression of Kell glycoprotein is high implying a key function in the early phases of erythropoiesis [29]. At the progenitor level, Maternal Kell antibodies decrease erythropoiesis in fetuses which lowers the number of reticulocytes associated with severe anemia as well as reduced bilirubin [30]. Kell alloimmunization may cause severe anemia and hydrops in newborn babies, due to early cell death before red blood cells collect sufficient hemoglobin levels (Fig:2), [31].
Uncommon Phenotypes Associated with KEL

*KEL* gene is highly polymorphic that encodes many KEL proteins.

1 Null Phenotype

Ko is an uncommon null phenotypic trait in the Kell system caused by a variety of KEL mutations, like improper splicing, nucleotide deletion, and premature stop codons, where Kell antigens are not present on RBCs. The health status of such phenotypic persons is good but when they come into contact with RBCs that contain Kell antigens, they create anti-Ku. Anti-Ku is associated with moderate to severe forms of transfusion reaction, resulting in the death of individuals possessing this phenotype. So, if a Ko person needs a blood transfusion, it is recommended to use only Ko blood components [32].

2 *K*\_MOD Phenotype

*K*\_mod is a hereditary RBC phenotype defined by low but detectable expression of Kell antigens with a high incidence [33]. Four *K*\_mod phenotypes *K*\_mod\-1 (1208G>A), *K*\_mod\-2 (2150A>G), *K*\_mod\-3 (1106T>C), and *K*\_mod\-4 (2227G>A) of were identified [34].

3 McLeod Phenotype

The Kell protein is chemically bonded to the XK protein which is hypothesized to perform the function of transportation, in the membrane of red blood cells [35]. When XK is missing, a disease known as McLeod syndrome develops, in which Kell antigens give very light expression and erythrocytes have abnormal spiny extensions (acanthocytosis). Muscular dystrophy, heart problem, mental abnormalities, and nervous system impairments such as malfunction of reflexes and balance abnormality are among the main results [36].

Methods Of Kel Blood Group Identification

Kell blood group is identified by two methods; (1) serological method and (2) genotyping method

1 Serological Method

To detect the antigens of a rare blood group system direct saline agglutination or indirect antiglobulin tests are used. Anti-K and -k chemicals (monoclonal antibodies IgM and IgG) are used in the tube for expanded blood group antigen typing (Diagast, Loos, France). This approach has the drawbacks of being very time taking and costly.
2 Genotyping Methods

Genotyping is critical for the identification of the blood groups of patients with multiple transfusions, detecting potential alloantibodies, and selecting antigen-negative RBCs for transfusion. Blood group genotyping is done using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), gene-specific primers using PCR, tetra-arms PCR, and next-generation sequencing (NGS). RFLP is an enzymatic process that identifies and separates DNA fragments of interest, while the tetra-arms PCR genotyping method use 4 primers in a single step, followed by gel electrophoresis. These KEL allele genotyping methods are accurate and useful in finding the expression of Kell antigens. It enables the identification of phenotypes when serology typing is unfeasible due to high cost or a lack of medical resources. Furthermore, this genetic analysis permits the identification of rare blood groups, such as KELL1/KELL2 and KELL3/KELL4, which could be important when blood is needed for all immunized patients with anti-KEL1 and -KEL3 antigens. The present study is aimed to review the uncommon Kell blood group to check the frequency of its antigens, and common and rare phenotypes associated with it all over the world.

Meta-Analysis

In this meta-analytic study, we have looked into many databases like Google Scholar, PubMed, JSTOR, Scopus, and Science Direct. For the collection of relevant data, different keywords are used such as ‘Kell blood group system’, ‘kell antigen’, ‘kell antibodies’, ‘hemolytic disease of the fetus and newborns’, ‘genetics’, and ‘epidemiology of kell antigen’. The titles and abstracts of the original research articles or reviewed papers are reviewed for screening of the data. Studies that did not match our inclusion criteria were excluded. The inclusion criteria are antigen and antibodies of the Kell blood group system, prevalence of kell antigens in different populations, and identification methods of the kell blood group system. All duplicates and irrelevant studies or papers were excluded. Out of 250 papers, and articles 60 papers are selected for this meta-analysis after screening and excluding irrelevant data (Fig: 3).

Epidemiology of Kell Blood Group Antigens

The present study consisted of data from 29 reported studies consisting of almost 20,000 individuals who were screened clinically or by molecular biological assays to find out mutations significantly associated with Kell antigens in different countries. Different parameters like prevalence, frequency, and incidence of different Kell antigens like KELL1/KELL2, KELL3/KELL4, and rarely KELL5/KELL6 were selected in the epidemiological study from 2000 to 2022 in the following countries: Africa, Brazil, Chile, China, Egypt India, Iran, Iraq, Korea, Malaysia, Nigeria, Oman, Pakistan, Portugal, Saudi Arabia, and Sudan. Most of the studies included are performed in Asian countries. The Kell antigen prevalence was almost the same in all the reported studies with KELL1 having the lowest frequency and KELL2 with the highest frequency.
Most of the research has been studied in India (2013, 2014, 2015, 2016, and 2018). From 2000 to 2022, most of the work was done during 2015, with only 1 publication in 2001, 2006, 2007, 2009, 2011, 2017, 2019, 2020, and 2021 and there is no reported study found in the years 2000, 2002, 2003, 2004, 2005, 2008 and 2010. The highest population size, selected in one of the reported studies was 3073 while the lowest population size, which is 100, was used in Pakistan, Portugal, Saudi Arabia, and Sudan. According to the results, the frequencies of *KEL1* are from zero (0) to the highest value of 11.87%, in all the reported studies and that of *KEL2* are from 34% to 100%. The frequencies of *KEL3* are between 0 to 2.6%, and that of *KEL4* are from 82.80% to 100% in all the studies reported (Table 2).

**Table 2: Epidemiology of KELL Antigens**
<table>
<thead>
<tr>
<th>S.N</th>
<th>Country</th>
<th>City</th>
<th>Study Period</th>
<th>Population Size</th>
<th>Frequency</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Africa</td>
<td>Cote d’Ivoire</td>
<td>2014</td>
<td>651</td>
<td>K1=0.77%</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K3=0.61%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K4=82.80%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Africa</td>
<td>South Africa</td>
<td>2015-2016</td>
<td>150</td>
<td>k1=4%</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>k2=84%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Brazil</td>
<td>São Paulo</td>
<td>2013</td>
<td>800</td>
<td>K1=2.2%</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K3=0.69%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K4=97.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K7=97.31%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Brazil</td>
<td>Paraná</td>
<td>2010</td>
<td>400</td>
<td>K1=0.28%</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=97.3%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Brazil</td>
<td>Brazil</td>
<td>2014</td>
<td>209</td>
<td>K1=0.24%</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=99.76%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Chile</td>
<td>Centro Productivo Regional de Sangre del Maule</td>
<td>2015</td>
<td>200</td>
<td>K1=4%</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>China</td>
<td>Xinjiang</td>
<td>2014-2015</td>
<td>158</td>
<td>K1=1.58%</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=98.42%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>China</td>
<td>Jiangsu</td>
<td>2012</td>
<td>146</td>
<td>K1=0%</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=100%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Egypt</td>
<td>Ismailia</td>
<td>2018</td>
<td>216</td>
<td>K1=23.6%</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=00</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>India</td>
<td>Delhi</td>
<td>2013</td>
<td>3073</td>
<td>K1=3.5%</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=99.97%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>India</td>
<td>Gujrat</td>
<td>2014</td>
<td>115</td>
<td>K1=6.09%</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K3=1.74%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K4=100</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>India</td>
<td>Delhi</td>
<td>2015</td>
<td>2769</td>
<td>K1=1.6%</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=98%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>India</td>
<td>Gujrat</td>
<td>2018</td>
<td>200</td>
<td>K1=2.5%</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=100%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Iran</td>
<td>Northeast of Iran</td>
<td>2011</td>
<td>522</td>
<td>K1=0%</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K3=0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K4=100%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>India</td>
<td>Jammu Kashmir</td>
<td>2015-2016</td>
<td>500</td>
<td>K1=2.6%</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=97.4%</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Korea</td>
<td>Seo-gu, Busan</td>
<td>2015-2017</td>
<td>382</td>
<td>K1=0%</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K3=0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K5=0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K4=100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K6=100%</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Malaysia</td>
<td>Malaysia</td>
<td>2006</td>
<td>594</td>
<td>K1=0.5%</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=99%</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Nigeria</td>
<td>Sokoto</td>
<td>2014</td>
<td>150</td>
<td>K1=2%</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=98%</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Oman</td>
<td>Oman</td>
<td>2019</td>
<td>337</td>
<td>K1=4.5%</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=99.4%</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Pakistan</td>
<td>Lahore</td>
<td>2015</td>
<td>192</td>
<td>K1=3.6%</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=96.3%</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Pakistan</td>
<td>Karachi</td>
<td>2014</td>
<td>100</td>
<td>K1=0%</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K2=100%</td>
<td></td>
</tr>
</tbody>
</table>
The mean values of Kell antigens \textit{KEL1} and \textit{KEL2} are 4.11 and 95.76 respectively. The mean values of \textit{KEL3} and \textit{KEL4} are 2.42 and 97.55 respectively (Fig: 4). This shows that \textit{KEL2} and \textit{KEL4} have high antigenic frequencies than \textit{KEL1} and \textit{KEL3} and the \textit{KEL4} antigen has the highest allelic frequency of all. The map (Fig. 5) describes the countries where the Kell antigens frequencies studies have been done. The colored portion of the map shows the respective country mentioned below the map. To the best of our knowledge, this is the first study to elaborate and thoroughly analyze peer-reviewed studies of Kell antigens all over the world.

### Conclusion

In immunohematology, antibodies to the Kell and Kx blood group systems pose a serological challenge. Kell blood group system has many antigens that are highly able to produce an immune response. As the anti-K, Js\textsuperscript{a}, Js\textsuperscript{b}, and Kb\textsuperscript{a} antibodies cause severe HDFN in pregnant women, so during pregnancy, it is important to do Kell typing in these women. The serological method for identification of the Kell blood group system is not commercially available and is also very expensive but the genotyping method is accurate, so it must be used to identify the kell blood system along with ABO typing to lower the chances of HDFN, and transfusion reaction. Given the high prevalence of anti-K HDFN, transfusion of K+ RBCs to pregnant women is questionable. The Kell-XK blood group systems are therapeutically and scientifically significant because Kell blood group antibodies do more than only attach to their cognate antigen. The antibody-mediated intracellular signaling processes that cause erythropoiesis suppression have yet to be identified. Anti-K HDFN protection, via passive immunization, is unlikely to be feasible. The discovery of immunodominant epitopes and a better knowledge of T-cell tolerance could guide to prevent HDFN.

### Declarations
Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and materials

- Data sharing is not applicable to this article as no datasets were generated during the current study.
- The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.
- The data included in this article has public access.

Competing interests

The authors declare that they have no competing interests

Funding

No funding agency participated in this study.

Authors' contributions

TK* Conceived and designed the experiments, MF* Wrote the paper, SN* Wrote the paper, SJ* Wrote the paper, SA* Wrote the paper, FS* Wrote the paper, UA* Collect the tables data, RS* Draw all the images, NN* Critically analyze the data, UM* Wrote the paper, NT2 analyze proofread the data, RS3 analyze proofread the data, Al4, construct the map.

All authors read and approved the final manuscript.

Acknowledgment

Nil

Author's information

Tasleem Kausar: tasleem.kausar@gscwu.edu.pk

Maham Fatima: mahammalikiub@gmail.com

Shumaila Noureen: shumailanoreen1234@gmail.com

Shumaila Javed: talhajaved3835@gmail.com
Sana Abdulsattar: sanach6591567@gmail.com
Fareeha Shahid: fareehashahid389@gmail.com
Umme Abiha: abihasherazi103@gmail.com
Rubina Shakeel: rubinashakil00786@gmail.com
Nadia Noureen: nadia.noureen@gscwu.edu.pk
Uzma Maqbool: druzma.maqbool@gscwu.edu.pk
Nabeela Tariq: nabeelatariq79@gmail.com
Rehan Sadiq Shaikh: rehansadiq80@yahoo.com
Amjad Islam Aqib: amjadislamaqib@cuvas.edu.pk

References


15. Dean L. The Kell blood group. In: Blood Groups and Red Cell Antigens [Internet]. National Center for Biotechnology Information (US); 2005.


63. Elsiddiq SI. Frequency of ABO, Rhesus (D) And Kell Antigens and Phenotypes in Alshaigia Sudanese tribe. Sudan University of Science and Technology; 2007.


Figures

Figure 1

The Structure of KEL Gene showing some common polymorphisms
Figure 2

Figure 3

Flow Chart of study selection for Meta-Analysis

Figure 4

Graphical presentation of mean value of Kell antigens
Study Area

Figure 5

Kell Antigen Frequencies in Studied Areas of the World

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx
- floatimage1.png