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

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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 have19 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

ISBT No.	Notation	Names	Exon	AA* Change	Frequency	References
KEL1	K	Kell	6	T 193 M	~2 - 25%	[12]
KEL2	K	Cellano	11	A 423 V	~100%	[13]
KEL3	Kp^a	Penny	8	Arg 281 Trp	~1.99%	[14]
KEL4	Kp^b	Rautenberg	-	-	~100%	[15]
KEL5	Ku	(K_0)			~100%	[15]
KEL6	Js^a	Sutter	17	Leu 597 Pro	~0.01%	[16]
KEL7	Js^b	Metthews	-	-	~100%	[15]
KEL8	Kw	-	-	-	~5%	[15]
KEL9	KL	Claas	-	-	~100%	[15]
KEL10	$U1^a$	Karhula	13	Glu 494 Val	~2%	[14]
KEL11	-	Côté	-	-	~100%	[15]
KEL12	-	Bockman	15	His 548 Arg	~100%	[13]
KEL13	-	Sgro	-	-	~100%	[15]
KEL14		Santini	-	-	~100%	[15]
KEL15	Kx	-	-	-	~100%	[15]
KEL16	-	-	-	-	~100%	[15]
KEL17	Wk^a	Weeks	8	Val 302 Ala	~0.3%	[14]
KEL18	-	Marshall	4	Arg 130 Trp	~100%	[13]
KEL19	-	Sublet	13	Arg 492 Gln	~100%	[13]
KEL20	Km	-	-	-	~100%	[15]
KEL21	Kp^c	Leves	8	Arg 281 Gln	~0.01%	[14]
KEL22	-	Ikar	9	Ala 322 Val	>99.9%	[13]
KEL23	-	-	10	Gln 382 Arg	~0.01%	[13]
KEL24	-	Clas	6	Arg 180 Pro	< 0.2%	[13]
KEL25	-	VLAN	-	-	Rare	[15]
KEL26	-	TOU	11	Arg 406 Gln	~100%	[13]
KEL27	-	RAZ	-	-	~100%	[15]

*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

S.N	Country	City	Study Period	Population Size	Frequency		References
1	Africa	Cote d'Ivoire	2014	651	K1=0.77% K3=0.61%	K2=99.84% K4=82.80%	[37]
2	Africa	South Africa	2015-2016	150	k1=4%	k2=84%	[38]
3	Brazil	São Paulo	2013	800	K1=2.2% K3=0.69% K6=2.69%	K2=97.8% K4=99.31% K7=97.31%	[39]
4	Brazil	Paraná	2010	400	K1=0.28%	K2=97.3%	[40]
5	Brazil	Brazil	2014	209	K1=0.24%	K2=99.76%	[41]
6	Chile	Centro Productivo Regional de Sangre del Maule	2015	200	K1=4%	K2=99%	[42]
7	China	Xinjiang	2014-2015	158	K1=1.58%	K2=98.42%	[43]
8	China	Jiangsu	2012	146	K1=0%	K2=100%	[44]
9	Egypt	Ismailia	2018	216	K1=23.6%	K2= 00	[45]
10	India	Delhi	2013	3073	K1=3.5%	K2=99.97%	[46]
11	India	Gujrat	2014	115	K1=6.09%, K3=1.74%	K2=100%, K4=100	[47]
12	India	Delhi	2015	2769	K1=1.6%	K2= 98.%,	[48]
13	India	Gujrat	2018	200	K1=2.5%	K2=100%	[49]
14	Iran	Northeast of Iran	2011	522	K1=0%, K3=0%,	K2=100%, K4= 100%	[50]
15	India	Jammu Kashmir	2015-2016	500	K1=2.6%	K2=97.4%	[51]
16	Korea	Seo-gu, Busan	2015-2017	382	K1=0%, K3=0%, K5=0%	K2=100%, K4=100%, K6= 100%	[52]
17	Malaysia	Malaysia	2006	594	K1=0.5%	K2=99%	[53]
18	Nigeria	Sokoto	2014	150	K1=2%	K2=98%	[54]
19	Oman	Oman	2019	337	K1=4.5%	K2=99.4%	[55]
20	Pakistan	Lahore	2015	192	K1=3.6%	K2=96.3%	[56]
21	Pakistan	Karachi	2014	100	K1=0%	K2=100%	[57]

22	Portugal	Portugal	2001	100	K1=2%	K2=34%	[58]
2023	Saudi Arabia	eastern region	2020	100	K1=8%	K2=92%	[59]
24	Saudi Arabia	Taraba	2014	399	K1= 9%, K3=2%	K2=99.9%, K4=99.9%	[60]
25	Saudi Arabia	Jeddah	2021	758	K1=12.3%, K3=2.6%	K2= 99.1%, K4= 100%	[61]
26	Saudi Arabia	Riyadh	2015	400	K1=18.2%, K3=11.7%	K2=97%, K4=96%	[62]
27	Sudan	Alshaigia	2007	100	k1=4%	k2=96%	[63]
28	Sudan	Ten tribes	2009	1000	k1=2%	k2=99.4%	[64]
29	Sudan	Khartoum State	2015	500	K1=0.03%	K2=0.97%	[65]

The mean values of Kell antigens *KEL1* and *KEL2* are 4.11 and 95.76 respectively. The mean values of *KEL3* and *KEL4* are 2.42 and 97.55 respectively (Fig: 4). This shows that *KEL2* and *KEL4* have high antigenic frequencies than *KEL1* and *KEL3* and the *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^a, Js^b, and Kb^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

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Authors' contributions

TK[1]* Conceived and designed the experiments, MF[1] Wrote the paper, SN[1] Wrote the paper, SJ[1] Wrote the paper, SA[1] Wrote the paper, FS[1] Wrote the paper, UA[1]Collect the tables data, RS[1] Draw all the images, NN[1]Critically analyze the data, UM[1] Wrote the paper, NT[2] analyze proofread the data, RS[3] analyze proofread the data, AI[4], construct the map.

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References

1. Garratty GJT.m.r., Blood groups and disease: a historical perspective. 2000. 14(4): p. 291–301.
2. Mitra R, Mishra N. and G.P.J.I.j.o.a. Rath. Blood groups systems. 2014;58(5):524.
3. Redman CM, et al. Kell blood group antigens are part of a 93,000-dalton red cell membrane protein. J Biol Chem. 1986;261(20):9521–5.
4. Reid ME, Lomas-Francis C, Olsson ML. The blood group antigen factsbook. Academic press; 2012.
5. Lee S, et al. Organization of the gene encoding the human Kell blood group protein. Blood. 1996;87(11):4922.
6. Storry J, et al. International society of blood transfusion working party on red cell immunogenetics and terminology: report of the Seoul and London meetings. ISBT Sci Ser. 2016;11(2):118–22.
7. Redman CM, Lee S. Kell blood group system and the McLeod syndrome. Molecular Basis of Human Blood Group Antigens, 1995: p. 227–242.
8. Moise KJ. Fetal anemia due to non-Rhesus-D red-cell alloimmunization. In: Seminars in fetal and neonatal medicine. Elsevier; 2008.
9. Lee S, et al., Organization of the gene encoding the human Kell blood group protein [published erratum appears in Blood 1996 Jun 1; 87 (11): 4922]. 1995.
10. Daniels G, et al. Blood group terminology 1995: ISBT working party on terminology for red cell surface antigens. Vox Sang. 1995;69(3):265–79.
11. Russo D, Redman C, Lee S. Association of XK and Kell blood group proteins. J Biol Chem. 1998;273(22):13950–6.
12. Lee S, et al., Molecular basis of the Kell (K1) phenotype. 1995.
13. Lee S. Molecular basis of Kell blood group phenotypes. Vox Sang. 1997;73(1):1–11.

14. Lee S, et al. Point mutations characterize KEL10, the KEL3, KEL4, and KEL21 alleles, and the KEL17 and KEL11 alleles. Transfusion. 1996;36(6):490–4.
15. Dean L. The Kell blood group. In: Blood Groups and Red Cell Antigens [Internet]. National Center for Biotechnology Information (US); 2005.
16. Redman C, Lee S. The Kell blood group system. Transfus Clin Biol. 1995;2(4):243–9.
17. Lee S, Russo D, Redman CM. The Kell blood group system: Kell and XK membrane proteins. In: Seminars in hematology. Elsevier; 2000.
18. Duguid JK, Bromilow IM. Haemolytic disease of the newborn due to anti-k. Vox Sang. 1990;58(1):69.
19. Smoleniec J, Anderson N, Poole G. Hydrops fetalis caused by a blood group antibody usually undetected in routine screening. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1994;71(3):F216–7.
20. Donovan L, et al. Hemolytic disease of the newborn due to anti-Jsa. Transfusion. 1973;13(3):153–3.
21. Stanworth S, Fleetwood P, De Silva M. Severe haemolytic disease of the newborn due to anti-Jsb. Vox Sang. 2001;81(2):134–5.
22. Shirey RS, King KE, Ness PM. Hemolytic transfusion reactions: Acute and delayed, in Blood Banking and Transfusion Medicine. Elsevier Inc; 2007. pp. 668–76.
23. Coleman S, et al., Alloimmunization in patients with sickle cell disease and underrecognition of accompanying delayed hemolytic transfusion reactions. 2019. 59(7): p. 2282–2291.
24. Sirianni G, et al., A retrospective chart review of transfusion practices in the palliative care unit setting. 2019. 36(3): p. 185–190.
25. Lin M, et al., Fatal hemolytic transfusion reaction due to anti-Ku in a Knull patient. 2003. 19(1): p. 19–21.
26. Gajjar K, Spencer CJTO, Gynaecologist. Diagnosis and management of non-anti-D red cell antibodies in pregnancy. 2009. 11(2): p. 89–95.
27. Daniels G, Hadley A, Green CA. Causes of fetal anemia in hemolytic disease due to anti-K. Transfusion. 2003;43(1):115–6.
28. Gabrilove J. Overview: erythropoiesis, anemia, and the impact of erythropoietin. In: Seminars in hematology. Elsevier; 2000.
29. Southcott MJ, Tanner MJ, Anstee DJJB, The Journal of the American Society of Hematology, The Expression of Human Blood Group Antigens During Erythropoiesis in a Cell Culture System: Presented in part as an abstract at the 39th American Society of Hematology Meeting, December 5–9, 1997 (Blood 90: 175b, 1997 [abstr, suppl 1, part 2]). 1999. **93**(12): p. 4425–4435.
30. Vaughan JI, et al., Inhibition of erythroid progenitor cells by anti-Kell antibodies in fetal alloimmune anemia. 1998. 338(12): p. 798–803.
31. Daniels G, Hadley A, Green CAJT. Causes of fetal anemia in hemolytic disease due to anti-K. 2003. 43(1): p. 115–116.

32. Lin M, et al. Fatal hemolytic transfusion reaction due to anti-Ku in a Knull patient. Immunohematology. 2003;19(1):19–21.
33. Marsh W, Redman C. The Kell blood group system: a review. Transfusion. 1990;30(2):158–67.
34. Lee S, et al. Mutations that diminish expression of Kell surface protein and lead to the Kmod RBC phenotype. Transfusion. 2003;43(8):1121–5.
35. Mohandas N, Narla A. Blood group antigens in health and disease. Curr Opin Hematol. 2005;12(2):135–40.
36. Bansal I, et al. Transfusion support for a patient with McLeod phenotype without chronic granulomatous disease and with antibodies to Kx and Km. Vox Sang. 2008;94(3):216–20.
37. Bogui LS, et al., Phenotypic profile of Rh and Kell blood group systems among blood donors in Cote d'Ivoire, West Africa. Journal of blood transfusion, 2014. **2014**.
38. Govender L, et al. Molecular red cell genotyping of rare blood donors in South Africa to enhance rare donor-patient blood matching. Afr J Lab Med. 2021;10(1):1–8.
39. Arnoni CP, et al. An easy and efficient strategy for KEL genotyping in a multiethnic population. Revista brasileira de hematologia e hemoterapia. 2013;35:99–102.
40. Guelsin GAS, et al. Genetic polymorphisms of Rh, Kell, Duffy and Kidd systems in a population from the State of Paraná, southern Brazil. Revista brasileira de hematologia e hemoterapia. 2011;33:21–5.
41. Flôres MALR, et al. Rh, Kell, Duffy, Kidd and Diego blood group system polymorphism in Brazilian Japanese descendants. Transfus Apheres Sci. 2014;50(1):123–8.
42. Rojas MV, et al., Frequency of antigens in Rh and Kell blood system in blood donors. Revista Cubana de Hematología, Inmunología y Hemoterapia, 2015. **31**(2): p. 160–171.
43. Lin G, et al. MNS, Duffy, and Kell blood groups among the Uygur population of Xinjiang, China. Genet Mol Res. 2017;16(1):1601–9176.
44. Zhong L, et al. Genotyping for Kidd, Kell, Duffy, Scianna, and RHCE blood group antigens polymorphisms in Jiangsu Chinese Han. Chin Med J. 2012;125(6):1076–81.
45. Swelem O, et al. ABO, RH phenotypes and kell blood groups frequencies in an Egyptian population. Omnia. 2018;6:2–2018.
46. Makroo R, et al. Prevalence of Rh, Duffy, Kell, Kidd & MNSs blood group antigens in the Indian blood donor population. Indian J Med Res. 2013;137(3):521.
47. Kahar MA, Patel RD. Phenotype frequencies of blood group systems (Rh, Kell, Kidd, Duffy, MNS, P, Lewis, and Lutheran) in blood donors of south Gujarat, India. Asian J Transfus Sci. 2014;8(1):51.
48. Garg N, et al., Phenotype Prevalence of Blood Group Systems (ABO, Rh, Kell) in Voluntary, Healthy Donors-Experience of a Tertiary Care Hospital in Delhi, North India. J Blood Disord Transfus 6: 297. doi: 10.4172/2155-9864.1000297 Page 2 of 4 J Blood Disord Transfus Rh Blood Group System ISSN: 2155–9864 JBDT, an open access journal. Minimum Maximum Mean Std. Deviation Age, 2015. **18**(55): p. 30.32.

49. Shah A, et al. Pattern of distribution of 35 red cell antigens in regular voluntary blood donors of South Gujarat, India. Transfus Apher Sci. 2018;57(5):672–5.
50. Keramati MR, et al. Blood group antigens frequencies in the northeast of Iran. Transfus Apheres Sci. 2011;45(2):133–6.
51. Yasmeen I, Sidhu M, Ahmed I, Distribution of RH and Kell (K) blood group antigens among blood donors in a tertiary care hospital of Jammu region, India. 2019.
52. Shin K-H, et al. Frequency of red blood cell antigens according to parent ethnicity in Korea using molecular typing. Annals of laboratory medicine. 2018;38(6):599–603.
53. Musa RH, et al. Red cell phenotyping of blood from donors at the National blood center of Malaysia. Asian J Transfus Sci. 2012;6(1):3.
54. Erhabor O, et al. Duffy red cell phenotypes among pregnant women in Sokoto, North Western Nigeria. J Blood Disord Transfus. 2014;5:7–11.
55. Al-Riyami AZ, et al. Prevalence of red blood cell major blood group antigens and phenotypes among Omani blood donors. Oman Med J. 2019;34(6):496.
56. Fatima S, et al, KELL BLOOD GROUP ANTIGENS IN THE BLOOD DONORS ATTENDING BLOOD BANKS OF TERTIARY CARE HOSPITALS OF LAHORE, PAKISTAN. Prof Med J. 2019;26(07):1167–71.
57. Karim F, et al. Rhesus and Kell Phenotyping of Voluntary Blood Donors: Foundation of a Donor Data Bank. J Coll Physicians Surg Pak. 2015;25(10):757760–760.
58. Araujo F, et al., Blood group antigen profile predicted by molecular biology-use of real-time polymerase chain reaction to genotype important KEL, JK, RHD, and RHCE alleles. IMMUNOHEMATOLOGY-WASHINGTON DC-, 2002. **18**(3): p. 59–64.
59. Owaidah AY, et al. Phenotype frequencies of major blood group systems (Rh, kell, kidd, duffy, mns, p, Lewis, and Lutheran) among blood donors in the eastern region of Saudi Arabia. J blood Med. 2020;11:59.
60. Mustafa MHI, et al., Distribution of Kell Blood Group System Antigens Kp, Kp b in Major Tribes of Turaba Province-KSA. Int. J. of Multidisciplinary and Current research, 2014.
61. Felimban RI, Sumeda SM. Distribution of Kell antigens K, k, Kpa, and Kpb among blood donors in Jeddah city of Western Saudi Arabia. Asian J Transfus Sci. 2021;15(1):75.
62. Elsayid M, et al. Phenotypic Profile of Kell blood group system among saudi donors at King Abdulaziz Medical City-Riyadh. J Med Sci Clin Res. 2017;5(1):15654–57.
63. Elsiddiq SI. Frequency of ABO, Rhesus (D) And Kell Antigens and Phenotypes in Alshaigia Sudanese tribe. Sudan University of Science and Technology; 2007.
64. Elmissbah T. Distribution of Kell blood group system antigens Kpa, Kpb, and phenotypes in major populations of Sudan. J Blood Disord Transfus. 2013;4(3):140–42.
65. Khogali AAM. Frequency of ABO and Rhesus-D blood group antigens and phenotypes among Sudanese blood donors in Central Blood Bank. In: Khartoum State. Sudan University of Science & Technology; 2015.

Figures

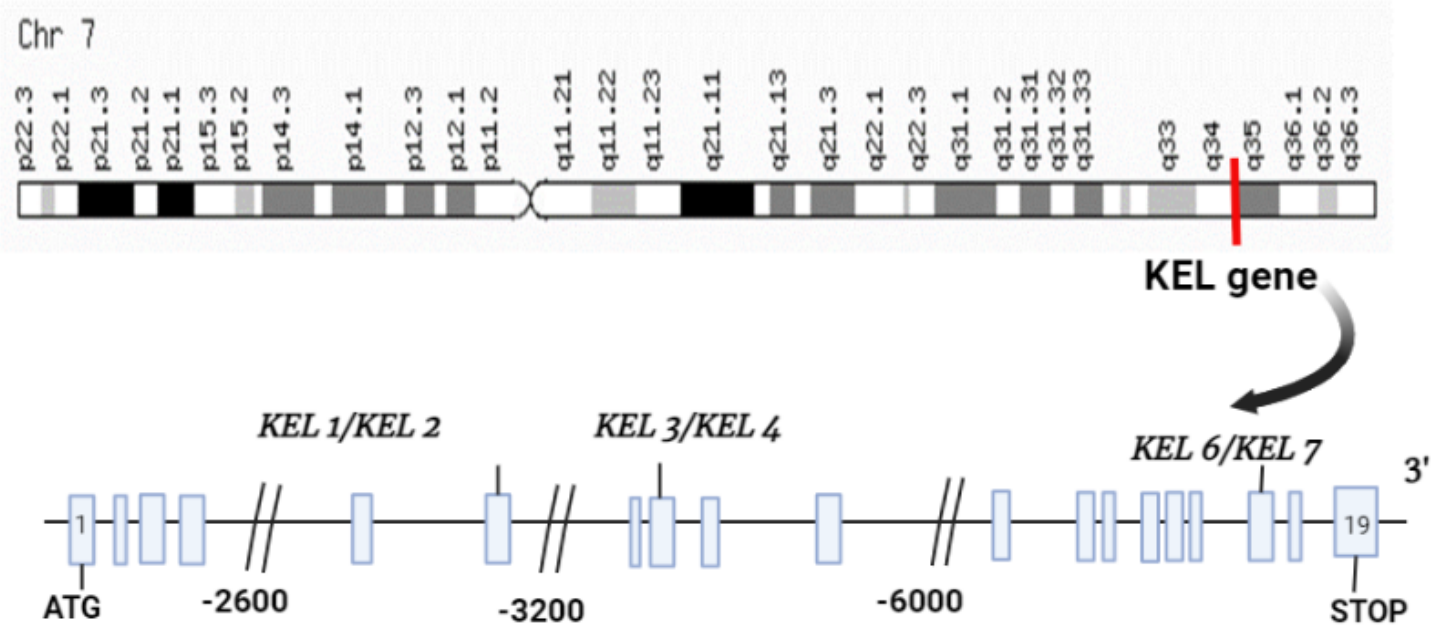

Figure 1

The Structure of KEL Gene showing some common polymorphisms

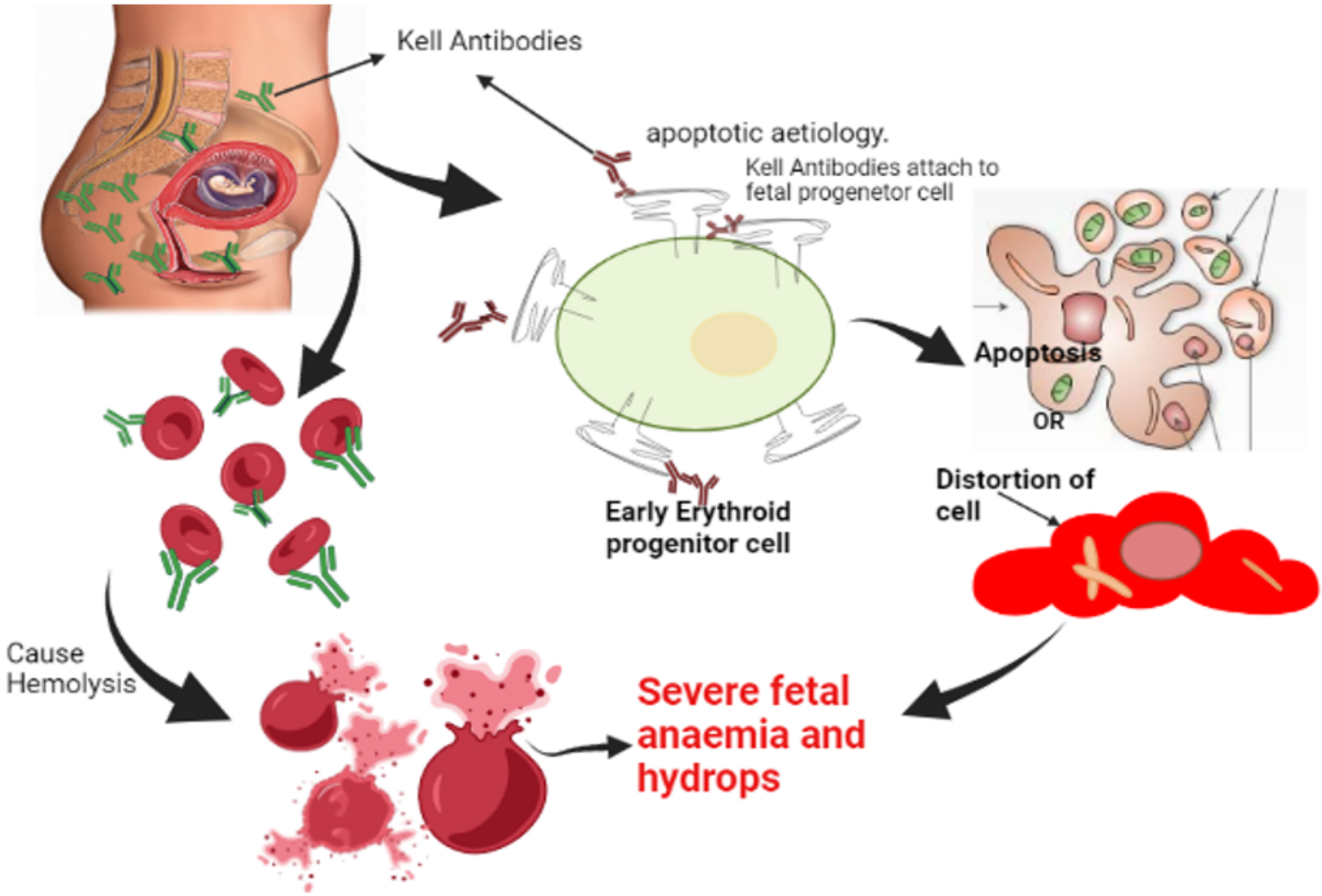

Figure 2

Kell alloimmunization: Anti-K, Immunoglobulin G, cause fetal anemia and hydrops.

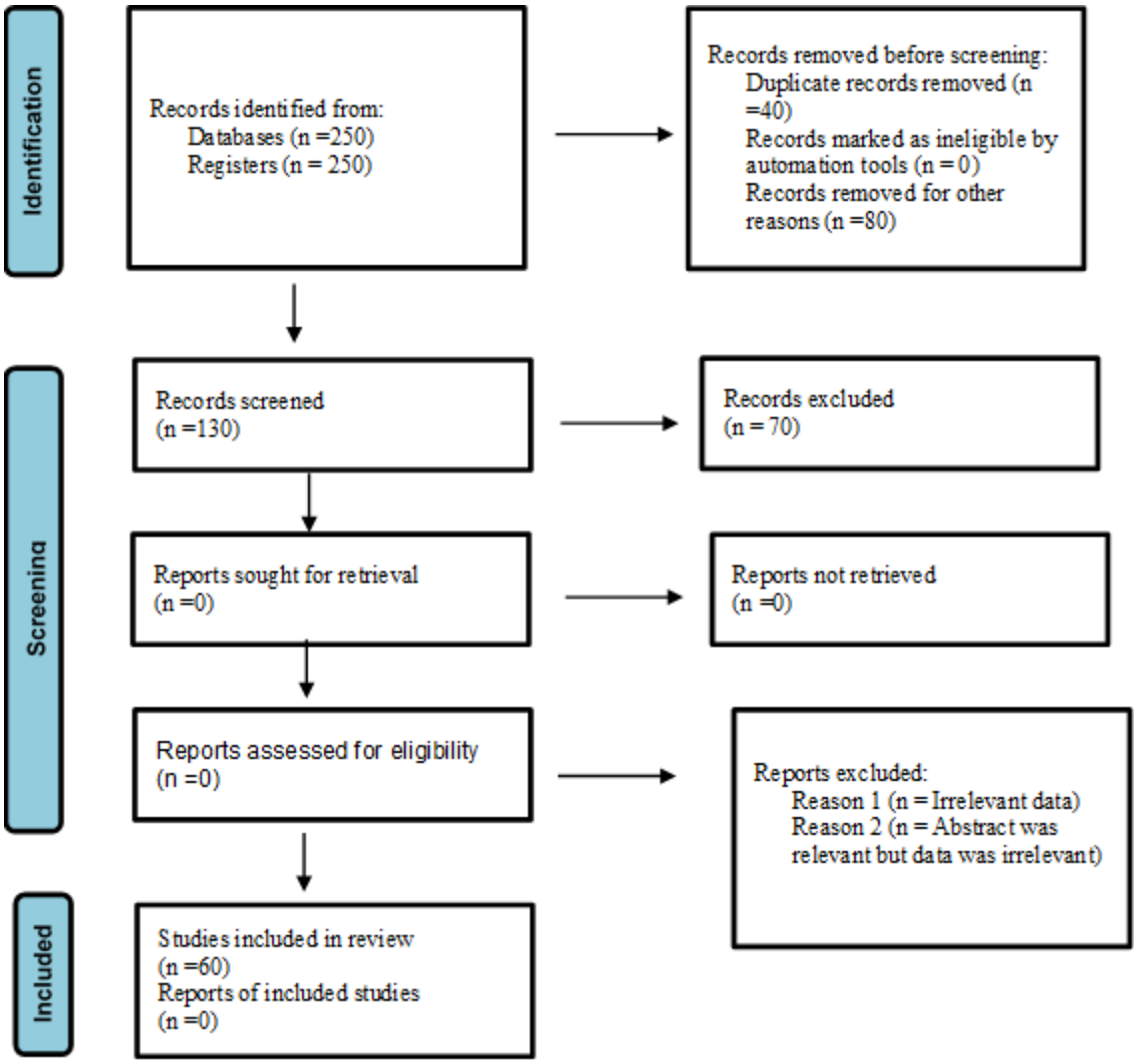

Figure 3

Flow Chart of study selection for Meta-Analysis

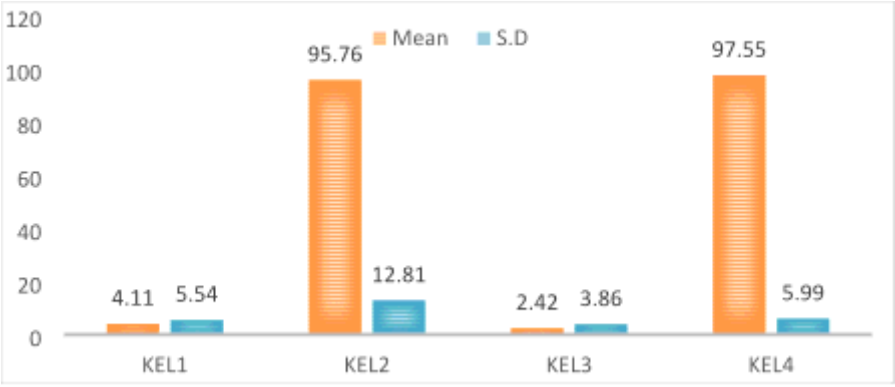

Figure 4

Graphical presentation of mean value of Kell antigens

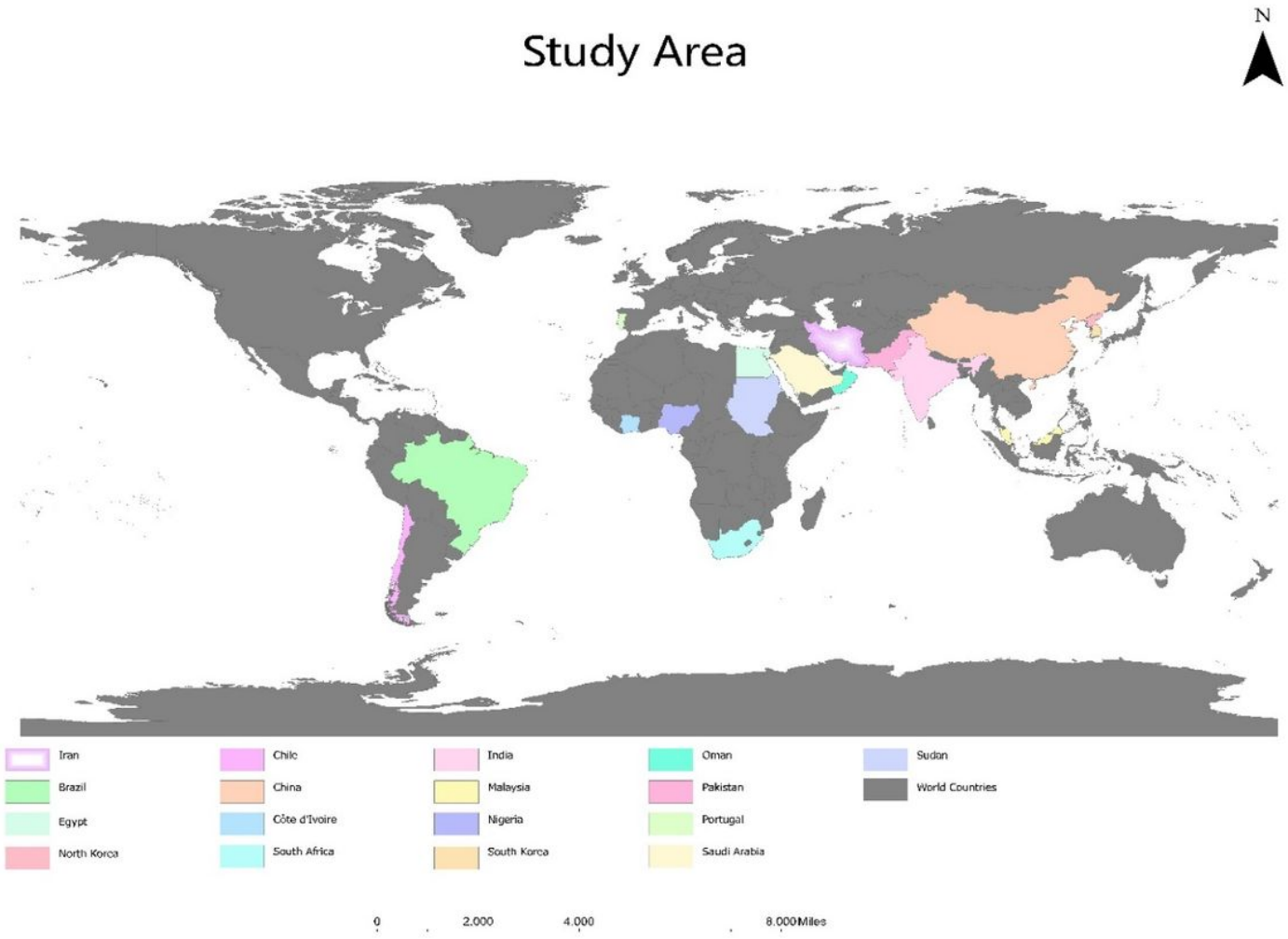

Figure 5

Kell Antigen Frequencies in Studied Areas of the World

Supplementary Files

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- PRISMA2020checklist.docx
- floatimage1.png