Transfusion Medicine Reviews 31 (2017) 165–172

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

The Kidd (JK) Blood Group System

Shaun Lawicki [a,b,*], Randal B. Covin [c], Amy A. Powers [a,b]

[a] John A. Burns School of Medicine University of Hawai'i at Mānoa UH Pathology Residency Program Office, Honolulu, HI
[b] Queens Medical Center, Honolulu, HI
[c] Blood Bank of Hawaii, Honolulu, HI

ARTICLE INFO

Available online 9 November 2016

Keywords:
Kidd blood group system
Transfusion medicine
Transfusion reaction
Blood donors
Erythrocyte membrane
Erythrocytes

ABSTRACT

The Kidd blood group system was discovered in 1951 and is composed of 2 antithetical antigens, Jk^a and Jk^b, along with a third high-incidence antigen, Jk3. The Jk3 antigen is expressed in all individuals except those with the rare Kidd-null phenotype. Four Kidd phenotypes are therefore possible: Jk(a+b−), Jk(a−b+), Jk(a+b+), and Jk(a−b−). The glycoprotein carrying the Kidd antigens is a 43-kDa, 389-amino acid protein with 10 membrane-spanning domains which functions as a urea transporter on endothelial cells of the renal vasa recta as well as erythrocytes. The *HUT11/UT-B/JK* (*SLC14A1*) gene encoding this glycoprotein is located on chromosome 18q12-q21. The Jk^a and Jk^b antigens are the result of a single-nucleotide polymorphism present at nucleotide 838 resulting in an aspartate or asparagine amino acid at position 280, respectively. The Kidd blood group can create several difficult transfusion situations. Besides the typical acute hemolytic transfusion reactions common to all clinically relevant blood group antigens, the Kidd antigens are notorious for causing delayed hemolytic transfusion reactions due to the strong anamnestic response exhibited by antibodies directed against Kidd antigens. The Kidd-null phenotype is extremely rare in most ethnic groups, but is clinically significant due to the ability of those with the Kidd-null phenotype to produce antibodies directed against the high-incidence Jk3 antigen. Anti-Jk3 antibodies behave in concordance with anti-Jk^a or anti-Jk^b possessing the capability to cause both acute and delayed hemolytic reactions. Antibodies against any of the 3 Kidd antigens can also be a cause of hemolytic disease of the fetus and newborn, although this is generally mild. In this review, we will outline the makeup of the Kidd system from its historical discovery to the details of the Kidd gene and glycoprotein, and then discuss the practical aspects of Kidd antibodies and transfusion reactions with an extended focus on the Kidd-null phenotype. We will end with a brief discussion of the donor aspects related to the screening and supply management of blood from donors with the rare Jk(a−b−) phenotype.

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The Kidd blood group system is a relatively straightforward entity with only 2 antithetical antigens, Jk^a and Jk^b, along with a third high-incidence antigen, Jk3. Jk3 is expressed in those with the Jk(a+b−), Jk(a−b+), and Jk(a+b+) phenotypes and is generally only of clinical

* Corresponding author at: Shaun Lawicki, MBBS, UH Pathology Residency Program Office, 1356 Lusitana St, 6th Fl, Honolulu, HI 96813.
E-mail addresses: lawicki@hawaii.edu (S. Lawicki), rcovin@bbh.org (R.B. Covin), aapowers@hawaii.edu (A.A. Powers).

http://dx.doi.org/10.1016/j.tmrv.2016.10.003
0887-7963/

significance in those with the rare Kidd-null phenotype, Jk(a−b−). Despite its apparent simplicity, the Kidd blood group can create several difficult situations for blood bankers and transfusionists. This review will outline the makeup of the Kidd system from its historical discovery to the details of the Kidd gene and glycoprotein, and then discuss the practical aspects of Kidd antibodies and transfusion reactions with an extended focus on the Kidd-null phenotype. Finally, the donor aspects related to the screening and supply management of blood from donors with the rare Jk(a−b−) phenotype are discussed.

History

The Kidd blood group was discovered in 1951 subsequent to a case of fatal erythroblastosis fetalis (hemolytic disease of the fetus and newborn [HDFN]) due to an antibody directed against an unknown antigen on the fetal red blood cells identified in the serum of an American parturient mother, Mrs Kidd, after delivery [1]. The antibody specificity was later found to be against the Jk^a antigen, which was named in memory of Mrs Kidd's lost child. Further testing with this antibody by the same group found that it reacted with 76% to 77% of red cells from those of European descent in both Boston and London, providing the first report of Kidd antigen prevalence [2]. The expected antithetical antibody, anti-Jk^b, was first reported 2 years later in England [3].

The Kidd-null phenotype, Jk(a−b−), was first described in 1959 when a case of jaundice after blood transfusion in a Filipino woman of Chinese and Spanish ancestry was encountered [4]. She had previously delivered 2 children without evidence of HDFN and had no history of abortions or previous blood transfusions. Her serum reacted with all red cells tested except for her own which were phenotyped as Jk(a−b−) based on negative reactions with multiple examples of anti-Jk^a and anti-Jk^b and confirmed by absorption testing. Determination of the exact antibody specificity with adsorption studies was described with residual reactions against Jk(a−b+) cells after adsorption with Jk(a+b−) cells but loss of reactions after adsorption with Jk(a−b+) cells. Eluates from the adsorbing cells reacted equally with Jk(a+b−) and Jk(a−b+) cells concluding that her serum contained a combination of anti-Jk^b and anti-Jk^aJk^b (currently anti-Jk3) antibodies. Given her lack of previous transfusions and her husband's Jk(a−b+) phenotype, it is most likely that she became immunized against the Kidd antigens during her previous pregnancies.

Kidd Glycoprotein and Gene

The function of the glycoprotein containing the Kidd antigens was suggested before the protein or gene was isolated due to the serendipitous discovery that the red cells of a Samoan man with aplastic anemia resisted lysis in 2 mol/L urea. He was found to have an elevated platelet count using an automated system that depended on urea lysis of erthyrocytes, whereas peripheral blood smear review showed no evidence of excessive platelets [5]. His red blood cells were not being effectively lysed and therefore were being counted as platelets by the automated system. He was found to have the Jk(a−b−) phenotype. Thus, the Kidd glycoprotein was assumed to have a urea transport function.

In 1987, the first isolation of the Kidd glycoprotein was accomplished using a dot-blot method using affinity-purified IgG anti-Jk^a, -Jk^b, and -Jk3 antibodies to yield a 45-kDa protein [6]. Then in 1994, a complementary DNA (cDNA) clone (*HUT11*) was isolated demonstrating that *HUT11* encodes a 43-kDa polypeptide which mediates urea transport [7]. The same group found that immunoprecipitation with anti-Jk3 isolated a 45- to 60-kDa glycoprotein from all red cells except those with the Jk(a−b−) phenotype. This molecular weight was reduced to 36 kDa after removal of *N*-glycosylation with *N*-glycanase [8]. This original *HUT11* sequence was later found to be a slightly aberrant transcript, with the correct cDNA for the erythrocyte urea transporter being identical except for a glutamic acid at position 44 in place of lysine and only 2 Val-Gly dipeptides instead of 3 after position 227 [9,10]. The *HUT11* gene product is a 43-kDa, 389-amino acid protein with 10 membrane-spanning domains, cytoplasmic N- and C-terminals, and *N*-glycosylation on the third extracellular loop at Asn211 which carries ABO antigens [11]. The *JK* glycoprotein is illustrated in the Figure.

The Kidd blood group gene locus was found to be linked to 2 different restriction fragment length polymorphisms assigned to chromosome 18 in 1987 [12,13]. After cloning *HUT11* and determining that it was the same as the Kidd protein, in situ hybridization was used to localize the Kidd locus to 18q12-q21 [8]. The *HUT11/UT-B/JK* (*SLC14A1*) gene is approximately 30 kilobases in length and includes 11 exons, with exons 4 to 11 representing the coding region [14].

The Kidd glycoprotein has been estimated to have approximately 14,000 antigen sites on red blood cells by immunoelectron microscopy with anti-Jk^a and ferritin-labeled antihuman IgG [15]. Besides the erythrocyte membrane, the transcript for the Kidd glycoprotein and urea transporter has been found in kidney, brain, heart, pancreas, prostate, bladder, testes, and colon tissues [16]. Two urea transporters have been identified within the human kidney. The Kidd glycoprotein, designated *UT-B*, is present on endothelial cells of the renal vasa recta as well as erythrocytes. *UT-A*, the second urea transporter present in human kidney, shares significant homology with *UT-B* and is only present on renal cells [13]. The vasa recta provides the vascular supply to the renal medulla, and renal urea transporters function to maintain the urea concentration and overall osmotic gradient within this area to allow for water conservation and urine concentration [17,18]. The main functions of the erythrocyte urea transporter are likely related to the fact that red blood cells must traverse the renal medulla because it is the only location they are typically exposed to high urea concentrations. Here it functions to facilitate rapid urea transport across the erythrocyte membrane to prevent cell shrinkage and swelling as it enters and leaves, respectively, the renal medulla. The rapid active transport of urea out of the red cell also averts decreasing the medullary urea concentration which would secondarily reduce the kidney's urine concentrating efficiency [19]. *UT-B* has also been described in human colonic epithelium where its urea transport may function to support the normal colonic microbiota [20,21].

Jk^a and Jk^b

The antithetical antigens Jk^a and Jk^b are inherited as the products of co-dominant alleles. The expression of Jk^a and/or Jk^b antigens is determined by a single-nucleotide polymorphism (SNP) within the *SLC14A1* gene, which confers a single amino acid difference between alleles. The sequence for expression of the Jk^b antigen is considered the reference allele, *JK*B* or *JK*02*, and has an adenine at nucleotide 838

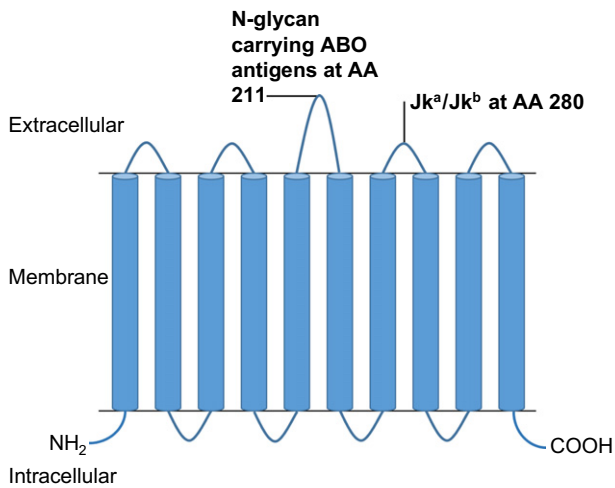

Figure. *JK* glycoprotein composed of 389 amino acids.

with an asparagine amino acid at position 280. The Jk^a antigen results from replacement of the adenine at nucleotide 838 with a guanine base resulting in an amino acid change to aspartate [22]. This amino acid difference at position 280 is located on the fourth extracellular loop of the JK protein. Given the simplicity of this antigen system, the Kidd blood group has been used as a model for genetic manipulation of erythroid precursors derived from cultured $CD34^+$ progenitor cells with the aim of producing designer red blood cells whose antigen expression profile is selectively chosen [23]. A lentivirus vector was used to transfect the cultured red cells with *JK* cDNA encoding either *JK*A* or *JK*B* alleles. This successfully transformed Jk(a+b−) or Jk(a−b+) cells into Jk(a+b+) cells. The investigators were also able to inhibit Jk^a and Jk^b expression below a serologically detectable level by introducing a shRNA that interferes with *JK* transcription. Use of this technology to produce reagent red cells with a particular antigen expression profile could be of great benefit for serological testing, and eventually, we may be able to custom design red cells for difficult patients with rare or multiple alloantibodies.

The phenotype frequencies for the Kidd system have been studied in many ethnic populations. The first estimates were made from populations of mostly whites of European descent. Using 6 series tested with anti-Jk^a in a population of 4275 Europeans, the following gene and genotype frequencies were reported: *JK*A* 0.5142, *JK*B* 0.4858, *JK*A/A* 0.2644, *JK*A/B* 0.4996, and *JK*B/B* 0.2360 [24]. Another early study on 2102 Canadians using both anti-Jk^a and anti-Jk^b found very similar gene frequencies of *JK*A* 0.5162 and *JK*B* 0.4838 [25]. The gene frequencies for many other populations have been collected and reported in the past [26]. The 1000 Genomes Project provides an open-access database of common human genetic variation for a diverse set of individuals from multiple populations. It contains the genomes of 2504 individuals from 26 populations obtained using a combination of low-coverage whole-genome sequencing, deep exome sequencing, and dense microarray genotyping [27]. The results for the Kidd system are presented in Table 1.

Another study of American donors using the Beadchip array to assess blood group antigen expression was performed with division of donors into various Asian ethnic groups as well as Native Americans and Pacific Islanders. Although the results showed up to a 10% variation in specific groups for at least one of the Kidd antigens in comparison to the white distribution, none of these results were significant and overall comparison of the study population vs whites showed no significant difference in Kidd antigen expression [28]. From this and the 1000 Genomes Project data, we can deduce that Asian and Hispanic populations do not differ greatly in gene and genotype frequencies in comparison to the white population. However, *JK*B* expression is much lower in the black population than in the other ethnic groups with a reciprocal increase in *JK*A* expression. Kidd phenotype distributions for whites, blacks, and Asians are available and summarized in Table 2.

Kidd antigen prevalence has also been reported in several specific ethnic groups worldwide that are not commonly represented in large studies in North America and Europe. These include the northern Indian population, which revealed a slightly increased gene expression for *JK*A* of 0.5835 and subsequent decrease in *JK*B* expression to 0.4165 when contrasted to whites [30]. These results have been confirmed in another Indian population as well as appearing as a trend across the South Asian cohort of the 1000 Genomes Project [27,31]. A study of Iranian blood donors found that they express *JK*A* in 79.1%, which is nearly equal to whites but had a small reduction in *JK*B* expression as it was seen in only 65.1% of this population resulting in a decrease in the Jk(a+b+) and Jk(a−b+) phenotypes and a subsequent increase in Jk(a+b−) [32]. An evaluation of the Kidd antigens among pregnant women in Nigeria revealed results in line with the prevalence data for blacks presented in Table 2 [33].

Table 1
Kidd blood group allele and genotype frequencies in ethnic populations from the 1000 Genomes Project [27]

Population	Allele: frequency (count)		Genotype: frequency (count)		
	Jk^a	Jk^b	Jk(a+b−)	Jk(a−b+)	Jk(a+b+)
All populations	0.589 (2950)	0.411 (2058)	0.367 (919)	0.189 (473)	0.444 (1112)
African	0.772 (1021)	0.228 (301)	0.596 (394)	0.051 (34)	0.352 (233)
African Caribbean in Barbados	0.760 (146)	0.240 (46)	0.562 (54)	0.042 (4)	0.396 (38)
African Ancestry in Southwest US	0.705 (86)	0.295 (36)	0.492 (30)	0.082 (5)	0.426 (26)
Esan in Nigeria	0.768 (152)	0.232 (46)	0.606 (60)	0.071 (7)	0.323 (32)
Luhya in Webuye, Kenya	0.742 (147)	0.258 (51)	0.545 (54)	0.061 (6)	0.394 (39)
Mandinka in The Gambia	0.841 (190)	0.159 (36)	0.717 (81)	0.035 (4)	0.248 (28)
Mende in Sierra Leone	0.747 (127)	0.253 (43)	0.518 (44)	0.024 (2)	0.459 (39)
Yoruba in Ibadan, Nigeria	0.801 (173)	0.199 (43)	0.657 (71)	0.056 (6)	0.287 (31)
American (Hispanic)	0.481 (334)	0.519 (360)	0.256 (89)	0.294 (102)	0.450 (156)
Colombian in Medellin, Colombia	0.484 (91)	0.516 (97)	0.245 (23)	0.277 (26)	0.479 (45)
Mexican Ancestry in Los Angeles, USA	0.484 (62)	0.516 (66)	0.234 (15)	0.266 (17)	0.500 (32)
Peruvian in Lima, Peru	0.418 (71)	0.582 (99)	0.188 (16)	0.353 (30)	0.459 (39)
Puerto Rican in Puerto Rico	0.529 (110)	0.471 (98)	0.337 (35)	0.279 (29)	0.385 (40)
East Asian	0.474 (478)	0.526 (530)	0.218 (110)	0.270 (136)	0.512 (258)
Chinese Dai in Xishuangbanna, China	0.446 (83)	0.554 (103)	0.226 (21)	0.333 (31)	0.441 (41)
Han Chinese in Beijing, China	0.510 (105)	0.490 (101)	0.262 (27)	0.243 (25)	0.495 (51)
Southern Han Chinese, China	0.462 (97)	0.538 (113)	0.181 (19)	0.257 (27)	0.562 (59)
Japanese in Tokyo, Japan	0.462 (96)	0.538 (112)	0.192 (20)	0.269 (28)	0.538 (56)
Kinh in Ho Chi Minh City, Vietnam	0.490 (97)	0.510 (101)	0.232 (23)	0.253 (25)	0.515 (51)
European	0.499 (502)	0.501 (504)	0.256 (129)	0.258 (130)	0.485 (244)
Utah Residents with Northern/Western European Ancestry	0.525 (104)	0.475 (94)	0.242 (24)	0.192 (19)	0.566 (56)
Finnish in Finland	0.495 (98)	0.505 (100)	0.253 (25)	0.263 (26)	0.485 (48)
British in England and Scotland	0.478 (87)	0.522 (95)	0.242 (22)	0.286 (26)	0.473 (43)
Iberian Populations in Spain	0.472 (101)	0.528 (113)	0.243 (26)	0.299 (32)	0.458 (49)
Toscani in Italy	0.523 (112)	0.477 (102)	0.299 (32)	0.252 (27)	0.449 (48)
South Asian	0.629 (615)	0.371 (363)	0.403 (197)	0.145 (71)	0.452 (221)
Bengali in Bangladesh	0.640 (110)	0.360 (62)	0.419 (36)	0.140 (12)	0.442 (38)
Gujarati Indian in Houston, Texas	0.709 (146)	0.291 (60)	0.495 (51)	0.078 (8)	0.427 (44)
Indian Telugu in the UK	0.662 (135)	0.338 (69)	0.451 (46)	0.127 (13)	0.422 (43)
Punjabi in Lehore, Pakistan	0.557 (107)	0.443 (85)	0.323 (31)	0.208 (20)	0.469 (45)
Sri Lankan Tamil in the UK	0.574 (117)	0.426 (87)	0.324 (33)	0.176 (18)	0.500 (51)

Table 2
Kidd phenotype distribution (% occurrence) [29]

	Whites	Blacks	Asians
Jk(a+b−)	26.3	51.1	23.2
Jk(a−b+)	23.4	8.1	26.8
Jk(a+b+)	50.3	40.8	49.1
Jk(a−b−)	Rare	Rare	0.9 (Polynesians)

Weak or Modified Kidd Alleles

Although the Kidd blood group system is considered relatively simple given the normal expression of just 2 different alleles, it has been discovered that multiple mutations in these alleles can result in antigens with a weak or modified expression profile. The first report in the literature of investigation into those with discrepant Kidd typing revealed multiple mutated alleles in both *JK*A* and *JK*B* [34]. This study analyzed samples from 4 individuals who were found to have conflicting phenotypes for the Kidd antigens when tested with polyclonal and monoclonal antibodies against Jk^a and Jk^b. Sequencing of the Kidd locus in these patients revealed 2 unique SNPs in *JK*A* (130G > A and 511 T > C) and one unique SNP in *JK*B* (548C > T). One of the patients with the *JK*A* 130G > A polymorphism also appeared to have a possible anti-Jk3 antibody. A study of 6 patients with discrepant typing for Jk^a found that they all possessed the *JK*A* 130G > A SNP and showed weakened expression of Jk^a and Jk3 by flow cytometric analysis [35]. They found that this reduced expression was substantial enough in homozygotes for them to be mistaken for Jk(a−b−), but interestingly, there was also a noticeable reduction in antigen expression in heterozygotes. By immunoblotting, they revealed that the weak *JK*01* allele protein product hindered expression of the normal *JK*01* protein suggestive of protein interaction during transport or in situ in the red cell membrane. This group also analyzed 300 controls from the 4 typical Kidd phenotypes and found that the *JK*01* 130G > A SNP was present in 4.2% of their white donors. By querying the HapMap database they were able to obtain prevalence data for this weak allele in many different ethnic groups and found that it is generally more prevalent in nonwhite groups with up to 45.7% prevalence in a group of Han Chinese. Many additional weak or modified Kidd alleles have now been identified with the International Society for Blood Transfusion currently listing five *JK*A* and two *JK*B* weak alleles [36].

The Kidd-Null Phenotype

The Jk(a−b−) or null phenotype is a rare entity with significant implications in transfusion medicine. The Kidd-null phenotype brings the third antigen, Jk3, of the Kidd blood group system into discussion. This is a high-prevalence antigen present in all individuals with expression of either Jk^a or Jk^b. Those lacking Kidd antigen expression can make an anti-Jk3 antibody that is clinically significant and reacts with all red blood cells except those from Jk(a−b−) donors.

After the previously described discovery that Jk(a−b−) individuals have red cells resistant to lysis in 2 mol/L urea, this fact has been widely used both to confirm the Kidd-null phenotype in suspected cases and as a method to screen blood donors for this rare phenotype. Given that the *JK* protein product functions as a urea transporter, this resistance to urea lysis is not an unsuspected consequence. In red cells with a functional Kidd antigen/urea transporter, the active transport of urea across its concentration gradient results in a large influx of urea and subsequently water by osmosis causing the cell to swell and lyse. Kidd-null cells lack a functional urea transporter, and therefore, they do not uptake urea rapidly and resist lysis. However, Kidd-null red cells will eventually lyse because there is still a slow exchange of urea directly across the cell membrane. It has been found that urea crosses the membrane approximately 1000 times slower in Jk(a−b−) cells [37]. Red blood cells with the common Kidd phenotypes completely lyse within 2 minutes in a 2 mol/L urea solution, whereas those from Kidd-null persons require at least 15 minutes. Expectedly, red cells from people heterozygous for a Kidd-null allele show urea lysis times intermediate of those with homozygous genes [38].

Despite the rare nature of this phenotype, it has been found in most ethnic groups worldwide with a significantly increased prevalence in certain ethnicities. The Kidd-null phenotype has been found to be most abundant within the Polynesian population. Among 17,300 random Polynesian blood donors screened with the urea lysis method and then confirmed by serologic testing, 47 (0.27%) were Jk(a−b−) Jk:−3 [39]. Further breakdown of this Polynesian group into specific island groups revealed the highest frequency among Niueans (1.4%) and Tongans (1.2%). With urea lysis screening, the Kidd-null phenotype frequency has been published for many ethnic groups including the following: Thai (0.02%) [40], Japanese (0.002%) [41], Taiwanese (0.023%) [42], Chinese (0.008%) [43], Chinese Han (0.019%) [44], and Finnish (0.03%) [45].

The molecular basis for the Kidd-null phenotype has been found to be due to 2 different mechanisms. The vastly more common basis has been found to be due to mutations often in the form of SNPs but also larger deletions that result in amino acid changes causing truncated or nonfunctional proteins that are not expressed. This type of Kidd-null phenotype is therefore referred to as a silent allele and inherited as a recessive trait. The second, less common basis is that of a dominantly inherited inhibitor gene. Two of 14 Jk(a−b−) patients in a Japanese population were discovered by urea lysis screening to be different from the others in 3 important ways [41]. First, family studies revealed a dominant mode of inheritance, with a Jk(a+b+) mother having 2 Jk(a−b−) daughters who both subsequently had Jk(a−b−) children. Second, the Jk(a−b−) appearing cells were able to bind anti-Jk^a, anti-Jk^b, and anti-Jk3 antibodies, although it took adsorption and elution testing to illustrate this phenomenon. Finally, these red cells were found to have a urea lysis time intermediate between those of a common Kidd phenotype and those from other Jk(a−b−) cells of the recessive type. A family study determined that the gene for this dominant inhibitor, named *In(Jk)*, is not located at the JK locus, although it has not yet been localized, and this dominant inhibitor has only been seen in a small number of individuals.

Because of the recessively inherited Kidd-null alleles being most common in Polynesian populations, it is not surprising that the molecular basis was initially investigated in this group. The most common mutation responsible for the null phenotype in this group and overall was found to be a guanine to adenine substitution in the invariant 3′ acceptor splice site of intron 5 of the *JK*B* allele [21,46]. This mutation, often referred to as the Polynesian mutation, results in loss of exon 6 transcription. Transfection of *Xenopus* oocytes with the abnormal transcript did not result in evidence of production of a normal or truncated Kidd glycoprotein. Molecular screening of 46 random Polynesian DNA samples found that the intron 5 g > a mutation was heterozygously present in 8 samples resulting in an 8.7% gene frequency and 0.75% frequency of the Jk(a−b−) phenotype. Although this is about 3 times more than what was found in a much larger study of Polynesians [39], the makeup of this small sample was dominated by specific islander groups such as Tongans, Niueans, and Samoans, who have been identified as having the highest prevalence of the Kidd-null phenotype. The same Polynesian intron 5 g > a mutation has been found in other Asian ethnic groups with the following allele frequencies: indigenous Taiwanese, 1%-8%; Fujians (China), 2.5%; Filipinos, 9%; and Indonesians, 1% [47].

A multitude of other mutations have been identified that result in a silent *JK*A* or *JK*B* allele now that genetic sequencing is conveniently and affordably available. The International Society for Blood Transfusion has assigned allele names for 10 and 14 mutations causing a silent *JK*A* and *JK*B*, respectively [36]. They are summarized in Table 3. The Blood Group Antigen Gene Mutation Database lists many additional mutations which bring about the Jk(a−b−) phenotype as well.

Table 3
Silent alleles of the Kidd blood group system

Allele	Nucleotide change	Exon/Intron	Amino acid change	Population	References
*JK*01 N.01*	Del exons 4 &5	Exon 4, 5	Initiation Met absent, no protein	English, Tunisian	73,74
*JK*01 N.02*	202C > T	Exon 5	Gln68Stop	American white	75
*JK*01 N.03*	582C > G	Exon 7	Tyr194Stop	Swiss	73
*JK*01 N.04*	956C > T	Exon 10	Thr319Met	African American, Thai	75,40
*JK*01 N.05*	561C > A	Exon 7	Tyr187Stop	African American, black Brazilian	76
*JK*01 N.06*	342-1 g > a	Intron 5	Exon 6 skipped	Asian Indian	77
*JK*01 N.07*	723delA	Exon 8	Ile262fs	Not specified	78
*JK*01 N.08*	866A > G	Exon 9	Asn269Ser	Not specified	36
*JK*01 N.09*	27_50del	Exon 4	Val10_Arg17del	African Americans	79
*JK*01 N.10*	811+ 5 g > a	Intron 8	Ala270fs	Chinese	43
*JK*02 N.01*	342-1 g > a	Intron 5	Exon 6 skipped	Polynesian, Asian, others	21,46
*JK*02 N.02*	342-1 g > c	Intron 5	Exon 6 skipped	Chinese	80
*JK*02 N.03*	222C > A	Exon 5	Asn74Lys	Chinese, Taiwanese	43,81
*JK*02 N.04*	663G > T	Intron 7	Leu223fs	French white	21
*JK*02 N.05*	723delA	Exon 8	Ile262fs	Hispanic American	75
*JK*02 N.06*	871 T > C	Exon 9	Ser291Pro	Finnish	46
*JK*02 N.07*	896G > A	Exon 9	Gly299Glu	Chinese, Taiwanese, Thai	40,43,44,81
*JK*02 N.08*	956C > T	Exon 10	Thr319Met	Indian	75
*JK*02 N.09*	191G > A	Exon 4	Arg64Gln	Japanese, African Americans	82,83
*JK*02 N.10*	194G > A	Exon 4	Gly65Asp	French Canadian	84
*JK*02 N.11*	499A > G, 512G > A	Exon 7	Met167Val, Trp171Ter	Chinese	43
*JK*02 N.12*	437 T > C, 499A > G	Exon 6, 7	Leu146Pro, Met167Val	Chinese	43
*JK*02 N.13*	499A > G, 536C > G	Exon 7	Met167Val, Pro179Arg	Chinese	43
*JK*02 N.14*	896G > A	Exon 9	Gly299Glu	Chinese, Taiwanese, Thai	40,43,81

Two descriptions of patients transiently converting to the Jk(a−b−) phenotype are present in the literature [48,49]. One case reported was an 85-year-old Russian woman with myelofibrosis and bleeding secondary to colonic carcinoma. During a 2-year period, her Kidd phenotype changed from Jk(a+b−) to Jk(a−b−) twice, and she was found to make anti-Jk3 during this period that resulted in a transfusion reaction when she received Jk(a+b−) units at a hospital that did not detect the anti-Jk3 in pretransfusion testing. She was consequently transfused uneventfully with 39 units of Jk(a−b−) blood. When her phenotype reverted to Jk(a+b−), the anti-Jk3 became undetectable, and she was transfused with 11 units of Jk(a+b−) blood without incident.

Clinical Significance of the Kidd Antigens

As described in detail previously, the Kidd protein functions as a urea transporter in the erythrocyte and vasa recta of the kidney that maintains the urea concentration in the renal medulla so that the kidney has the ability to maximally concentrate urine. Considering this fact, one would not be surprised that a urine concentrating defect has been identified in Kidd-null patients. Fortunately, this defect is not substantial enough to be clinically important [37]. Kidd-null individuals also appear to have no other ill health effects, and their red cells are of normal shape and life-span [50]. Because of an unknown mechanism, those who are homozygous for *JK*A* have been found to have higher levels of total cholesterol than *JK*B* homozygotes or heterozygotes [51]. However, no difference in high-density lipoprotein or triglycerides is seen. This could be due to a closely linked gene and not the *JK* gene directly.

Outside clinical transfusion challenges presented by the Kidd blood group, the most significant clinical aspect of the Kidd system may be its implication in kidney transplant rejection as minor histocompatibility antigens. Both anti-Jk^a and anti-Jk^b have been associated with acute rejection of renal transplants which may be of the severe vascular or plasma cell-rich variants [52,53]. A single-center, retrospective study of 370 renal transplants described more interstitial inflammation in Kidd-mismatched grafts when compared with matched grafts [54]. These reports and findings have made it reasonable to avoid blood product transfusion whenever possible before transplantation to avoid the possibility of alloimmunization and to consider a screen for anti-Kidd antibodies in transplant patients with acute rejection.

The Kidd Blood Group System and Transfusion

The identification of anti-Jk^a and/or anti-Jk^b in routine clinical practice is relatively straightforward using standard serological techniques. These antibodies are most often IgG and detected using an indirect antiglobulin test, although weak examples may require use of enzyme-treated cells for detection. A dosage effect is often observed, with homozygous cells reacting more strongly with the antibody compared with heterozygous cells. Solid-phase testing has also been shown to be more sensitive for the detection of Kidd antibodies in line with its generally increased sensitivity overall [55].

Identification of an anti-Jk3 is more difficult, and the medical technologist must consider the possibility of this antibody early in the workup of a sample exhibiting a pattern of reactivity consistent with an antibody to a high-frequency antigen. Patients will typically present with a panreactive antibody screen and panel at the indirect antiglobulin test phase. In the absence of a recent transfusion or concomitant red blood cell autoantibody, the DAT and autocontrol will be negative. A full-antigen phenotype should be performed, and an anti-Jk3 must be suspected in patients who phenotype as both Jk^a and Jk^b antigen negative. In the absence of other red blood cell antibodies, no reactivity should be seen in screening cells lacking both the Jk^a and Jk^b antigens. Because screening cells lacking both of these antigens are scarce, it is often not possible to rule out the presence of additional alloantibodies without doing further adsorption steps. Screening cells used for adsorption should be phenotypically identical to the patient, but must be Jk^a and/or Jk^b positive to allow removal of the anti-Jk3. The adsorbed plasma may then be tested against a panel of selected cells to rule out any other alloantibodies that the patient may be at risk for developing. The decision to use cells for adsorption that are heterozygous or homozygous for either Jk^a or Jk^b does not appear to be critical. The detection of an additional anti-Jk^a or Jk^b, in addition to the anti-Jk3, is not required, because the antigens will be avoided during the provision of Jk3-negative blood.

The identification of an anti-Jk3 in a recently transfused patient is more complicated. In patients experiencing a delayed serologic or hemolytic transfusion reaction due to an anti-Jk3, the serological picture may be easily mistaken for a warm autoantibody, although discriminating immunohematologists may observe a mixed field reactivity in the DAT and autocontrol. These tests may also be negative in individuals who have already destroyed the incompatible transfused red cells.

Given the higher prevalence of the Jk3-negative phenotype in Hawaii, the possibility of an anti-Jk3 is considered in any recently transfused patient with a previous negative antibody screen who present with a serologic picture that appears consistent with a warm autoantibody. Kidd typing performed on pretransfusion samples consistent with a Jk3-negative phenotype and lack of reactivity with Jk3-negative screening cells is diagnostic. If the laboratory does not have sufficient Jk(a−b−) reagent red cells to eliminate the possibility of other concomitant alloantibodies, adsorption studies are required to rule out additional alloantibodies.

Even when using highly sensitive antibody detections methods, Kidd antibodies can be notoriously difficult to detect in pretransfusion testing due to their tendency to drop to undetectable levels in the plasma over time. It is often for this reason that Kidd antibodies are implicated in both immediate and delayed hemolytic transfusion reactions (DHTRs), with DHTRs being more common [56,57]. Anti-Jk^a has been the most commonly implicated among the Kidd system and may be responsible for more than one-third of DHTRs [58]. Review of the records of 8535 patients who had received transfusions found 34 patients who developed delayed serologic transfusion reactions. Nine (29%) of which occurred due to Kidd antibodies. Among the 34 delayed serologic transfusion reactions, 6 patients were considered to have had DHTRs, and 5 of these were determined to have occurred due to anti-Jk^a [59]. Fortunately given its commonality, anti-Jk^a most commonly results in mild to moderate hemolytic reactions; however, severe reactions are encountered and have been reported to result in significant morbidity [55,60,61]. Anti-Jk^b and anti-Jk3, though moderately and significantly less common, respectively, are more often associated with severe hemolytic reactions both immediate and delayed [56,62]. Although conflicting literature exists [63], IgG Kidd antibodies are generally felt to be capable of fixing complement and causing intravascular and extravascular hemolysis [59]. In fact, 40% to 50% of sera with Kidd antibodies have been found to have the ability to fix complement [64]. Of note, the DAT in hemolytic transfusion reaction due to Kidd antibodies may show positivity for complement only. Anti-Jk^a has also been implicated in hemolytic transfusion reactions where no antibody could be detected despite extended testing with high sensitivity detection methods. These patients have responded well to phenotypically matched red blood cell transfusions [65-67].

Cases of hemolytic transfusion reactions related to Kidd antigens can usually be managed with supportive care and simple transfusions of antigen-negative blood once the antibody specificity has been established. However, in severe cases when acute renal failure due to circulating free hemoglobin may occur, therapeutic plasma exchange has been used to successfully remove free hemoglobin and potentially reduce the Kidd antibody burden [68].

In addition to hemolytic transfusion reactions, HDFN has been reported in those with antibodies directed against the Kidd antigens. Overall, HDFN due to anti-Kidd is usually mild, although severe and even fatal case reports are in the literature [4,69-71]. Kidd-related HDFN may behave in a synergistic manner to increase the severity of fetal anemia when present with another cause of fetal anemia such as thalassemia [72]. Although a thorough discussion of HDFN management is outside the context of this review, most cases related to Kidd antibodies can be monitored with serial antibody titers and fetal ultrasounds if titers are high or increasing. A bilirubin scan (ΔOD450) can be performed on amniotic fluid samples if the risk of fetal anemia is considered elevated. Intrauterine transfusion may be required in severe cases, although this is exceedingly rare in cases due to Kidd antibodies.

Blood Donor Screening and Supply Management

Provision of blood negative for Jk^a or Jk^b is generally without difficulty due to the relatively common prevalence of the Jk(a−b+) and Jk(a+b−) phenotypes in most ethnic groups. In contrast, it is difficult to procure Jk(a−b−) blood due to the rarity of this phenotype. Because blood donor screening can be time-consuming and expensive, especially when screening for rare phenotypes, most blood banks will need to turn to a rare donor registry to find acceptable antigen-negative units. Because of the ethnic distribution of blood donors in Hawaii (a high percentage of Polynesian and Southeast Asian donors), the Blood Bank of Hawaii screens all new donors for the Jk3-negative phenotype using the urea lysis test. When a donor's red cells are found to be resistant to urea lysis, they are serologically confirmed as Jk(a−b−). These donors are encouraged to donate frequently and approach their siblings about blood donation. In addition, they are considered rare donors, and after donation, their red cells are placed in a rare donor inventory. If not needed immediately for transfusion, the red cells are frozen in 40% glycerol where they may be stored for up to 10 years at less than or equal to −65°C. With approval of the medical director, extremely rare units may be stored longer than 10 years. Because of the rarity of this phenotype, the knowledge that these units will be transfused to Jk3-negative patients, and that frozen units will be deglycerolized removing most of the antibody, the Blood Bank of Hawaii does allow donors with an anti-Jk3 to donate blood. These units are tagged appropriately with the known antibody.

Several national and international rare donor programs exist because of the difficulty procuring blood products for patients with multiple alloantibodies, antibodies to high-frequency antigens, and null phenotypes. In the United States, the American Rare Donor Program, which is jointly managed by the American Red Cross and the AABB, is usually consulted initially when rare donor products are needed and local suppliers cannot be found. Worldwide requests may be submitted to the International Rare Donor Panel, a joint initiative of the World Health Organization and the International Society for Blood Transfusion that is located in Bristol, United Kingdom. The American Rare Donor Program and International Rare Donor Panel maintain large databases of rare donors and store rare null red cells, with the goal of facilitating reference laboratory identification of difficult antibodies and fulfilling the subsequent need for rare donor products. Through these programs, both fresh and frozen units of rare null red cells may be obtained; however, it should be kept in mind that most requests yield a limited number of compatible units.

Conclusion

In summary, the Kidd blood group system is a clinically significant red blood cell antigen system composed of 2 antithetical antigens, Jk^a and Jk^b, as well as a third high-incidence antigen, Jk3. Antibodies directed against any of these 3 antigens are capable of causing acute or delayed hemolytic transfusion reactions as well as HDFN. Antibodies directed against Kidd antigens are also notoriously anamnestic and often may be detectable only with high-sensitivity methods or only discovered after a delayed hemolytic reaction. The null phenotype lacking production of any of the 3 antigens, though exceedingly rare, has been described in most ethnic groups worldwide. There is, however, an increased prevalence of the null phenotype among certain ethnicities including Polynesians/Pacific Islanders and Southeast Asians. Those with the null phenotype may produce an antibody to the high-incidence Jk3 antigen necessitating the requirement of rare antigen-negative blood for transfusion. These rare donor blood products can be difficult to procure and may require consultation with the American Rare Donor Program or International Rare Donor Panel to obtain.

In the future, our knowledge about the Kidd blood group system is most likely to expand due to the increasingly common molecular sequencing of the *JK/SLC14A1* gene. Therefore, we can expect a consistent stream of newly discovered weak and null alleles to be discovered. The increasing convenience and decreasing cost of sequencing are also likely to make it a more frequently used tool in cases of discordant serological or phenotypic results. Genome-wide association studies have and may continue to find SNPs in the *JK/SLC14A1* gene that are related to increased risk of bladder cancer or other diseases/neoplasms [85,86].

Another line of potential research may be to investigate the significance of the IgG subclass of Kidd antibodies. This may be especially important in HDFN where subclass may be more predictive of hemolytic risk than antibody titers.

Conflict of Interest

None of the authors have any conflicts of interest, financial or otherwise, to disclose in relation to the Kidd blood group system or any other content contained in this manuscript.

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