9 Kidd Blood Group System

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9.1 Introduction

Jk[a] (JK1) and Jk[b] (JK2) of the Kidd system are the products of alleles and are polymorphic in all populations tested. The Jk[a]/Jk[b] polymorphism is associated with an Asp280Asn substitution in the Kidd glycoprotein. Kidd antibodies are often difficult to work with and are potentially dangerous, as they are a common cause of delayed HTRs.

A rare null phenotype, Jk(a–b–), is generally inherited recessively and is most commonly found in Polynesians. Jk(a–b–) cells lack the high incidence antigen Jk3. A variety of mutations are responsible for Jk(a–b–).

The Kidd glycoprotein functions as a urea transporter.

The *JK* (*SLC14A1*) locus is on chromosome 18 at 18q11-q12.

9.2 The Kidd glycoprotein and the gene that encodes it

Before the Kidd glycoprotein had been purified or the *JK* gene cloned, failure of Jk(a–b–) red cells to lyse in 2 *M* urea led to the supposition that the Kidd glycoprotein might be a red cell urea transporter (Section 9.4.2). A red cell membrane structure of apparent MW 45 kDa was isolated by affinity purified IgG anti-Jk[a], -Jk[b], and -Jk3 bound to nylon membranes [1]. Immunoprecipitation with anti-Jk3 isolated a glycoprotein of 46–60 kDa from red cells of all phenotypes except Jk(a–b–) [2]. The MW was reduced to 36 kDa by removal of *N*-glycosylation with *N*-glycanase [2]. Jk(a+b–) red cells were estimated to have around 14 000 Jk[a] antigen sites by immunoelectron microscopy with anti-Jk[a] and ferritin labelled anti-human IgG [3]. This is compatible with an estimate of less than 32 000 sites per cell obtained by determining the quantity of a mercurial required to inhibit facilitated urea transport [4].

Olivès *et al.* [5] produced a cDNA probe from human erythroblast mRNA by reverse transcriptase PCR with primers derived from the amino acid sequence of a rabbit urea transporter. They used this probe to isolate a cDNA clone (*HUT11*) by screening a human bone marrow library. A 36 kDa polypeptide produced by coupled *in vitro* transcription-translation of the cDNA was immunoprecipitated by anti-Jk3. Immunoblotting with a rabbit antibody raised to peptides predicted from the cDNA sequence revealed 46–60 kDa components from human red cell membranes, except those of the Jk(a–b–) phenotype [2]. *HUT11* has subsequently been shown to be an aberrant transcript or a cloning artefact [6]. Another transcript (*HUT11A*) encoding glutamic acid in place of lysine at position 44 and two Val-Gly dipeptides instead of three after position 227, produces the Kidd glycoprotein and red cell urea transporter [6,7]. The predicted gene product is a 43 kDa, 389 amino acid polypeptide with about 63% identity with the rabbit urea transporter. The protein contains 10 potential membrane-spanning domains, with intracellular N- and C-terminals, and is *N*-glycosylated at Asn211 on the third extracellular loop, the glycan expressing ABO activity [8] (Figure 9.1). In addition to erythroid cells and kidney, the Kidd transcript was also found in brain, heart, pancreas, prostate, bladder, tested, intestine, and colon tissues [9].

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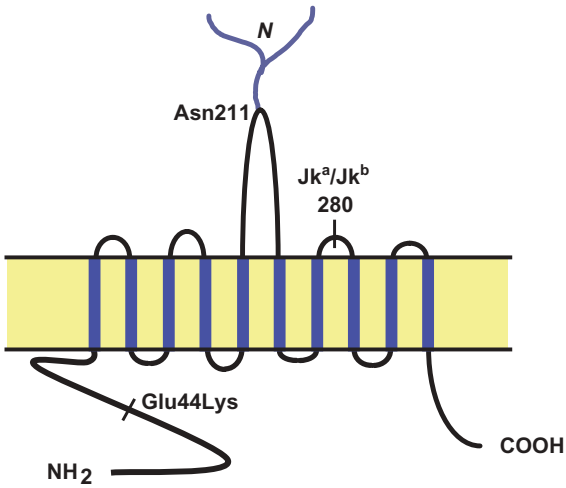

Figure 9.1 Diagrammatic representation of the Kidd glycoprotein in the red cell membrane, showing 10 membrane-spanning domains, cytoplasmic N- and C-termini, a single *N*-glycan on the third extracellular loop at Asn211, the position of the Jk[a]/Jk[b] polymorphism on the fourth extracellular loop, and the position of Glu44Lys associated with weak Jk[a] and Jk3 expression.

Table 9.1 Organisation of the *JK* (*SLC14A1*) gene.

Exon	Size (bp)	Amino acids	Intron size (kb)	
			[10]	[11]
1	93		0.7	
2	64		2.4	
3	157		3.1	
4	172	1–50	0.6	0.543
5	190	51–113	3.55	3.0
6	129	114–156	1.9	2.0
7	193	157–221	2.5	2.5
8	148	222–270	0.27	0.217
9	135	271–315	8.6	9.0
10	50	316–332	1.4	1.4
11	551	333–389		

The *JK* (*SLC14A1*) gene has 30 kb and contains 11 exons [10,11]. Exons 1–3 and part of 4 represent the 3′ untranslated region; exons 4–11 encode the mature protein (Table 9.1). The transcription initiation site is 335 bp upstream of the translation start codon in exon 4. The region between nucleotides −837 and −336 contains erythroid-specific GATA-1 and Sp1 transcription-factor binding sites, plus TATA and inverted CAAT boxes [10]. Two equally abundant erythroid transcripts, of 4.4 and 2.0 kb, have been identified, the smaller arising from skipping of exon 3 [8].

The Kidd gene, *SLC14A1*, and *SLC14A2*, a gene encoding another urea transporter (UT-A), were both localised to chromosome18q by *in situ* hybridisation [3,9].

9.3 Jk[a] and Jk[b] (JK1 and JK2)

An antibody in the serum of an American woman, Mrs Kidd, was named anti-Jk[a] in 1951 by Allen *et al.* [12], from the initials of Mrs Kidd's sixth child, who showed signs of HDFN. The antibody reacted with the red cells of 77% of Bostonians. The anticipated antithetical antibody, anti-Jk[b], was found in England two years later by Plaut *et al.* [13].

9.3.1 Frequency of Jk[a] and Jk[b]

Jk[a] and Jk[b] are inherited as the products of co-dominant alleles. The following phenotype frequencies were obtained from six series of tests with anti-Jk[a] on a total of 4275 Europeans [14]: Jk(a+), 76.4%; Jk(a–), 23.6%. The following gene and genotype frequencies are derived from these figures: *JK*A* 0.5142, *JK*B* 0.4858; *JK*A/A* 0.2644, *JK*A/B* 0.4996, *JK*B/B* 0.2360. Very similar gene frequencies were obtained from tests with anti-Jk[a] and -Jk[b] on red cells from 2102 Canadians: *JK*A* 0.5162, *JK*B* 0.4838 [14,15]. Numerous other population studies, many conducted with anti-Jk[a] only, have been summarised [16,17]. The gene frequency of *JK*A*, usually about 50% in Europeans, rises to 75% in some parts of Africa, but this frequency is by no means representative of all African populations. The frequency of *JK*A* is around 30% in Chinese and falls to as low as 20% in some Japanese studies, but this low frequency does not occur throughout Asia.

Table 9.2 shows genotype frequencies on four populations of American blood donors, obtained by molecular testing [18].

9.3.2 The molecular basis of the Kidd polymorphism

The Jk[a]/Jk[b] polymorphism results from 838G>A in exon 9, encoding Asp280Asn on the fourth extracellular loop of the Kidd glycoprotein [19] (Figure 9.1). Jk[a]/Jk[b] is also associated with a silent 588G>A SNP in exon 7 and

Table 9.2 Kidd genotype frequencies on four populations of American blood donors, obtained by testing on the BeadChip array [18].

		Genotypes		
Ethnic group	No. tested	*JK*A/A*	*JK*A/B*	*JK*B/B*
Caucasians	1243	0.30	0.44	0.26
African Americans	690	0.54	0.37	0.09
Hispanic	119	0.36	0.42	0.22
Asian	51	0.22	0.53	0.25

another SNP at position −46 from the 3′ end of intron 9 [11]. G838 of *JK*A* introduces an *Mnl*I restriction site [6]. The 838G>A polymorphism can be interrogated in a variety of ways to provide reasonably reliable phenotype predictions [20]. In populations with a relatively high level of the most common silent allele (*JK*02N.01*), however, it may also be prudent to test for the IVS5−1g>a inactivating mutation to avoid false prediction of Jk(b+) (see Section 9.4.1).

Aberrant expression of Jk^a and Jk^b in two *JK*A/B* African Americans was associated with mutations in *JK* exon 7: 511T>C, Trp171Arg in *JK*01W.02* and 548C>T, Ala183Val in *JK*02W.01*, respectively [21]. Both amino acid changes are within the third extracellular loop. Another allele responsible for weak Jk^a is described in Section 9.4.6.

The Jk^a/Jk^b polymorphism was used as a model for the production of 'designer' red cells by genetic modification of erythroid cells cultured from $CD34^+$ progenitors. [22]. Transfection of the cultured cells with lentiviral vectors containing *JK* cDNA representing *JK*A* or *JK*B* alleles, converted Jk(a−b+) or Jk(a+b−) cells, respectively, to Jk(a+b+) red cells. On the other hand, lentiviral transfer of shRNA designed to interfere with *JK* transcription, reduced expression of Jk^a and Jk^b antigens, so that they were not detectable by routine serological testing. This technology clearly has great potential for the production of reagent red cells that express antigens of choice.

9.3.3 Effect of enzymes and reducing agents

Jk^a, Jk^b, and Jk3 are papain-, ficin-, trypsin-, chymotrypsin-, and pronase-resistant; treatment of red cells with these enzymes generally enhances reactivity with Kidd antibodies. Kidd antigens are not affected by sialidase or by AET.

9.3.4 Development and distribution of Kidd antigens

Jk^a and Jk^b are well developed on the red cells of neonates. Fetal cells have the same distribution of Kidd phenotypes as that found in the adult population. Jk^a and Jk^b antigens have been detected on red cells of 11- and 7-week-old fetuses, respectively [23].

Kidd antigens were not detected on lymphocytes, monocytes, granulocytes, or platelets [24–27]. Jk3 first appears on erythroblasts at a late stage of erythropoiesis [28].

9.3.5 Anti-Jk^a and -Jk^b

9.3.5.1 Alloantibodies

Anti-Jk^a and -Jk^b are often encountered in transfusion practice, with anti-Jk^a being more common than anti-Jk^b. They are most commonly detected within a month of transfusion, but then decline rapidly, often becoming undetectable after 3 months [29]. Jk^a and Jk^b are traditionally considered of relatively low immunogenicity, but when antibody evanescence is taken into account their calculated immunogenicity is substantially increased [30]. The only reports of 'naturally occurring' Kidd antibodies are anti-Jk^a in two Jk(a−b+) 9-month-old non-identical twins, detectable only by a solid-phase method [31], and an IgG anti-Jk^a in a 7-month-old boy with an *Escherichia coli* urinary tract infection [32]. Anti-Jk^a has been found during the first pregnancy of an untransfused woman [33] and a case of anti-Jk^a sensitisation following amniocentesis and intrauterine transfusion is reported [34]. Anti-Jk^a production appears to be associated with an *HLA-DRB1*01* genotype [35,36].

Kidd antibodies are often difficult to detect. Some directly agglutinate antigen-positive cells, but the reactions are usually weak by this method. Generally an antiglobulin test is required to detect Kidd antibodies. Use of enzyme-treated cells may be necessary to detect weaker antibodies. Anti-Jk^a detectable only by the manual Polybrene test was responsible for an HTR, emphasising the importance of detecting weak Kidd antibodies. Many anti-Jk^a react more strongly with Jk(a+b−) than with Jk(a+b+) cells, and some anti-Jk^a can only be detected with Jk(a+b−) cells [37]; some anti-Jk^b also demonstrate dosage. Panels for screening patient sera for antibodies should, therefore, contain Jk(a+b−) and Jk(a−b+) red cells.

Kidd antibodies are usually IgG or a mixture of IgG and IgM; they are rarely pure IgM [38,39]. Most IgG anti-Jk^a are IgG3 or a mixture of IgG3 and IgG1, and occasionally IgG1 alone. IgG2 may also be present. Four anti-Jk^b contained IgG1; one also contained IgG3 and one IgG4 [39,40]. Around 40–50% of sera containing Kidd antibodies bind complement; some Kidd antibodies can only be detected in the antiglobulin test when polyspecific antiglobulin or anti-complement is used [41,42]. Some Kidd antibodies may not be detectable by techniques incorporating a diluent that binds calcium [43]. Only those Kidd sera with an IgM component are capable of complement-binding as IgG Kidd antibodies are unable to fix complement [42].

9.3.5.2 Clinical significance

Kidd antibodies, which are often difficult to detect, are a hazard in blood transfusion. Anti-Jk^a has been responsible for severe and fatal immediate HTRs [44–48] and is regularly associated with delayed HTRs, which may be severe, leading to oliguria, renal failure, and even death [49,50]. Anti-Jk^b has also been incriminated in severe delayed HTRs [51–53]. A major reason why Kidd antibodies are such a common cause of delayed HTRs is their tendency to fall rapidly to low or undetectable levels in the plasma [29,30]. Pineda *et al.* [49,54] estimated that over one-third of delayed HTRs were caused by anti-Jk^a. Antigen-negative red cells should be selected for transfusion to patients with Kidd antibodies.

In an unusual case, a Jk(a–b+) patient with chronic lymphocytic leukaemia was found to have alloanti-Jk^b 14 days after transfusion of two units of Jk(b+) red cells [55]. The transfused red cells clearly survived in the patient and the DAT was negative, but Jk^b could not be detected in the patient's blood. It has been suggested that this represents a case of alloantibody induced antigen loss [56].

In contrast to the haemolytic activity of Kidd antibodies in incompatible blood transfusion, Kidd antibodies are only very rarely responsible for severe HDFN, though there are a few reports of severe and fatal HDFN caused by anti-Jk^a [57] and -Jk^b [58–60].The reason why Kidd antibodies so rarely cause HDFN, even when present in relatively high titre, is unclear.

There are two reported cases of passenger lymphocyte syndrome caused by anti-Jk^a, following peripheral blood progenitor cell transplantation, one causing severe haemolysis [61] and the other non-haemolytic [62].

Kidd may be a minor histocompatibility antigen. Anti-Jk^a has been implicated in a severe vascular rejection of a kidney transplant [63]. An analysis of 370 renal transplants in a single centre suggested that Jk^a/Jk^b mismatched grafts had more interstitial inflammation than matched grafts [64].

9.3.5.3 Autoantibodies

Several cases of autoanti-Jk^a associated with AIHA have been described [65–70]. Red cells of one patient, who also developed idiopathic thrombocytopenic purpura (Evans syndrome), were initially typed as Jk(a–b+), but later became Jk(a+b+), their true phenotype as demonstrated by family study [70]. AIHA in a Jk(a+) patient taking Aldomet (methyldopa), with anti-Jk^a in her serum and in an eluate from her red cells, declined on cessation of the drug and the autoantibody gradually disappeared [66]. A Jk(a+b+) patient taking chlorpropamide, a hypoglycaemic agent, had an apparent anti-Jk^a in her serum and acute AIHA [68]. In a post-transfusion specimen the anti-Jk^a only reacted with Jk(a+b+) cells in the presence of chlorpropamide or related structures and the AIHA declined when chlorpropamide administration was stopped.

Autoanti-Jk^a has also been found in healthy individuals [71]. Four examples of benign autoanti-Jk^a reacted preferentially with red cells in the presence of parabens or certain other neutral aromatic compounds, the antibodies being detected because of the presence of parabens as preservatives in commercial low ionic-strength solutions [72,73].

A Jk(a–b+) nephrectomy patient who had suffered from chronic proteus infections showed signs of an HTR, although no transfusion had taken place [74]. The patient's serum contained autoanti-Jk^b. Jk(b–) red cells incubated with *Proteus mirabilis* reacted with anti-Jk^b reagents.

9.3.5.4 Monoclonal antibodies

IgM human monoclonal anti-Jk^a and -Jk^b have been produced by Epstein-Barr virus-transformation of lymphocytes from immunised donors and fusion with mouse myeloma cells to form heterohybridomas [75,76]. Some of these antibodies make excellent blood grouping reagents.

9.4 Jk(a–b–) phenotype and Jk3 antigen

The Kidd-null phenotype, Jk(a–b–), was first described by Pinkerton *et al.* in 1959 [77]. A Filipino woman of Chinese and Spanish ancestry, with two children, became

Table 9.3 Frequency of Jk(a–b–) phenotype in several populations, ascertained through screening by the urea lysis test.

Population	No. tested	No. Jk(a–b–)	Frequency (%)	References
Polynesian	17 300	47	0.272	[75]
Thai	25 340	5	0.020	[79]
Japanese	648 460	12	0.002	[80]
Taiwanese	95 451	22	0.023	[81]
Chinese	201 194	16	0.008	[82]
Chinese Han	100 000	19	0.019	[83]
Finnish	79 349	24	0.030	[84]
New Zealand Caucasian	120 000	0		[85]
English	52 908	0		[86]

jaundiced after blood transfusion. Her serum reacted with all cells save her own, which had the novel phenotype Jk(a–b–). Adsorption of her serum with Jk(a+b–) cells left some activity for Jk(a–b+) cells, but adsorption with Jk(a–b+) cells removed all antibody. Eluates from the adsorbing cells reacted with Jk(a+b–) and Jk(a–b+) cells. Thus, her serum contained a mixture of anti-Jk3 and anti-Jk^b.

9.4.1 Jk(a–b–) and *JK* silent alleles

Although rare in much of the world, many examples of Jk(a–b–) have been found in many different ethnic groups. Often they have been ascertained through the production of anti-Jk3. Jk(a–b–) is most abundant amongst Polynesians. Of 17 300 random Polynesian blood donors screened by the urea lysis method (Section 9.4.2) and confirmed serologically, 47 (0.27%) were Jk(a–b–) Jk:–3 [78]. The highest frequency was found in Niueans and Tongans, with 1.4% and 1.2% Jk(a–b–), respectively [78].The urea lysis method has been used to search for Jk(a–b–) in other ethnic groups (Table 9.3).

Homozygosity or compound heterozygosity for a variety of inactivating mutations in the *JK* gene have been responsible for Jk(a–b–) phenotype (Table 9.4). Others have been found in individuals of common Kidd phenotype through apparent discrepancy between genotype and serological result. The most common, often called the Polynesian mutation, is g>a in the invariant 3′ acceptor splice site of intron 5 of a *JK*B* allele (*JK*02N.01*), causing loss of exon 6 from mRNA transcripts [10,11]. The predicted, truncated Kidd glycoprotein could not be detected in *Xenopus* oocytes transfected with the abnormal transcript. Of 46 Polynesians, eight were heterozygous for the intron 5 mutation, a gene frequency of 8.7%, which predicts an incidence of 0.76% for Jk(a–b–) [11]. The same mutation was also found in Asians with the following allele frequencies: indigenous Taiwanese, 1–8%; Fujians (China), 2.5%; Filipinos, 9%; Indonesians, 1% [94].

Screening of 674 Black Brazilians for a mutation encoding Tyr187Stop (*JK*01N.05*), initially found in a Jk(a–b–) African American, disclosed one homozygote and five heterozygotes (gene frequency 0.52%) [90].

9.4.2 The urea lysis test for Jk(a–b–) phenotype

The urea lysis test for detecting Jk(a–b–) phenotype was discovered serendipitously when a Samoan man with aplastic anaemia appeared to have excessively high platelet counts in an automated system dependent on lysing red cells with 2 *M* urea [85]. These false platelet counts were shown to be due to failure of his Jk(a–b–) red cells to lyse. Red cells of common Kidd phenotypes lysed within one minute in 2 *M* urea; Jk(a–b–) red cells required at least 30 minutes for lysis. Red cells of individuals heterozygous for a null allele demonstrated intermediate lysis time in a modified urea lysis test [95].

9.4.3 Anti-Jk3

Anti-Jk3, the typical antibody of immunised Jk(a–b–) individuals, may be accompanied by separable anti-Jk^a or anti-Jk^b [77,96,97]. Only a minority of immunised Jk(a–b–) people produce anti-Jk3 [80,98]. An apparently 'naturally occurring' IgM anti-Jk3 was found in an untransfused Jk(a–b–) male, the only reported example;

Table 9.4 Some *JK* alleles responsible for Jk(a–b–) phenotype.

Allele symbol	Nucleotide change	Exon / intron	Amino acid change	Population	Refs
*JK*01N.01*	del exons 4 & 5	4, 5	Initiation Met absent	English, Tunisian	[87,88]
*JK*01N.02*	202C>T	5	Gln68Stop	American Caucasian	[89]
*JK*01N.03*	582C>G	7	Tyr194Stop	Swiss	[87]
*JK*01N.04*	956C>T	10	Thr319Met	African American	[89]
*JK*01N.05*	561C>A	7	Tyr187Stop	African American, Black Brazilian	[90]
*JK*02N.01*	IVS5–1g>a	Intron 5	Exon 6 skipped	Polynesians, Asians, others	[10,11]
*JK*02N.02*	IVS5–1g>c	Intron 5	Exon 6 skipped	Chinese	[91]
*JK*02N.03*	222C>A	5	Asn74Lys	Chinese, Taiwanese	[82,92]
*JK*02N.04*	IVS7+1g>t	Intron 7	Exon 7 skipped; fs, Leu223Stop	French Caucasian	[10]
*JK*02N.05*	723delA	8	fs, Ile262Stop	Hispanic American	[89]
*JK*02N.06*	871T>C	9	Ser291Pro	Finnish	[11,93]
*JK*02N.07*	896G>A	9	Gly299Glu	Chinese, Taiwanese, Thais	[79,82,83,92]
*JK*02N.08*	956C>T	10	Thr319Met	Indian	[89]

fs, frameshift.

his Jk(a–b–) sister had been pregnant seven times without making anti-Jk3 [99].

Jk3 antibodies react optimally by an antiglobulin test, the reaction being enhanced by enzyme treatment of the cells. Enzyme-treated cells may be haemolysed by anti-Jk3 in the presence of fresh serum [100]. Anti-Jk3 are usually IgG. Like other Kidd antibodies, anti-Jk3 may decline rapidly *in vivo* [96].

Anti-Jk3 has been responsible for severe immediate [101] and delayed [96,98,102] HTRs. Most babies of mothers with anti-Jk3 are clinically unaffected, although the baby's red cells may give a positive DAT, and in a few cases phototherapy was administered [97,98,103].

Two examples of autoanti-Jk3, or mimicking autoanti-Jk3, have occurred during pregnancy [104,105]. In one, which was associated with AIHA, mimicking autoanti-Jk^b was also present [104]. Autoanti-Jk3 may block Jk^a and Jk^b antigen sites, resulting in false serological results [106]. Anti-Jk3 in a patient with transient Jk(a–b–) phenotype is described in Section 9.4.5.

9.4.4 Jk(a–b–) of the dominant type

Red cells from two of 14 Jk(a–b–) Japanese blood donors found by the urea lysis test (Section 9.4.2) proved to be different from those of the other 12 and from Jk(a–b–) cells previously reported [80]. A family study suggested a dominant mode of inheritance: the presence of a Jk(a+b+) mother of two Jk(a–b–) daughters, both with Jk(a–b–) children, excludes homozygosity of a silent gene. The dominant inhibitor gene proposed to account for these observations was named *In(Jk)*, as it was considered analogous to *In(Lu)* of the Lutheran system (Section 6.8). Two further examples have been found in Japan. The molecular basis for In(Jk) remains unknown.

Jk(a–b–) red cells of the dominant type can bind anti-Jk3 and anti-Jk^a and/or anti-Jk^b, as detected in adsorption and elution tests. Kidd genotypes deduced in this way demonstrated that *In(Jk)* is not inherited at the *JK* locus. In(Jk) cells are less readily lysed in the urea lysis test than cells of common Kidd type and less resistant to lysis than Jk(a–b–) cells of the recessive type [80].

9.4.5 Transient Jk(a–b–)

An 85-year-old Russian woman with myelofibrosis and bleeding secondary to colon carcinoma was found to be Jk(a–b–) and to have anti-Jk3, which was responsible for a severe HTR [101]. Neither anti-Jk^a nor -Jk^b could be adsorbed and eluted from her red cells. Two years later her cells appeared to have a normal Jk(a+b–) phenotype and no anti-Jk3 or -Jk^b was present.

9.4.6 A *JK*A* allele responsible for a Jk_{mod} phenotype

A *JK*A* allele containing 130G>A in exon 4 (*JK*01W.01*), encoding Glu44Lys in the cytoplasmic N-terminal domain of the Kidd glycoprotein, was responsible for

reduced expression of Jk^a and Jk3 [21,107]. *JK*01W.01* also contained the 588G and intron 9 –46g, silent SNPs usually associated with *JK*B*. *JK*01W.01* homozygotes display substantial weakening of Jk^a and Jk3 and could be mistaken for Jk(a–b–), but weakened Jk^a and Jk3 were also apparent in *JK*A/01W.01* and *JK*B/01W.01* heterozygotes [107]. Such a dramatic effect of a glutamic acid to lysine substitution in the cytoplasmic domain might be unexpected, but analogies are seen in other blood groups, for example Fy^x (Section 8.3.4) and some D variants (Section 5.6). Furthermore, deletion of the cytoplasmic N-terminal domain, or just mutation of both Cys25 and Cys30 to serines, abolished membrane expression in oocytes, demonstrating the vital role of the N-terminal to successful localisation in the plasma membrane [8]. Immunoblotting indicated that the *JK*01W.01*-encoded protein hinders expression of the normal protein in heterozygotes, suggesting interaction between the proteins either in the membrane or during transport to the membrane, although the Kidd glycoprotein is generally considered monomeric red cell [107].

*JK*01W.01* is not rare in Caucasians: screening of 300 Swedish donors for 130A revealed an allele frequency of 4.2% [107].

9.5 The Kidd glycoprotein is the red cell urea transporter UT-B

Failure of Jk(a–b–) red cells to lyse in aqueous solutions of urea provided the first clue that the Kidd glycoprotein might function as a urea transporter (Section 9.4.2). Red cell lysis in the presence of urea results from an osmotic imbalance. In cells of common Kidd phenotype urea is transported very rapidly across red cell membranes, so in 2 *M* urea these cells rapidly take up urea, become hypertonic, and lyse because of the rapid diffusion of water into the cell. Jk(a–b–) red cells lack the Kidd glycoprotein. They take up urea slowly and, therefore, lyse very slowly in 2 *M* urea. Treatment of normal red cells with a mercurial inhibitor of urea and water transport resulted in a substantial retardation of lysis in 2 *M* urea (aqueous solution) [108]. Measurements of unidirectional urea and thiourea fluxes revealed that urea crosses the membrane of Jk(a–b–) red cells about 1000 times slower than normal cells [109].

The Kidd glycoprotein, UT-B, has substantial sequence homology with another human urea transporter (UT-A), present only on renal cells [9]. Physiological levels of expression of UT-B cDNA in *Xenopus* oocytes strongly facilitated urea transport, but not water permeability [6]. This activity is blocked by the urea transport inhibitors [5].

The Kidd glycoprotein is present on endothelial cells of the vasa recta, the vascular supply of the renal medulla, but is not present in renal tubules [110]. Urea transporters in the kidney play an important role in concentrating urea in the renal medulla, whilst conserving water, in order to produce concentrated urine [111]. UT-B in human colon epithelium could participate in the transport of urea across the colon mucosa and assist in the maintenance of a normal colonic bacterial population [112,113]. In red cells, UT-B has two main functions:

1 transporting urea rapidly in and out of the cells to prevent shrinkage as they pass through the high urea concentration of the renal medulla, and to prevent swelling as they leave;

2 to prevent the red cells from carrying urea away from the renal medulla, which would decrease the urea concentrating efficacy of the kidney [114].

The Kidd-null phenotype is not associated with any clinical defect, although, like UT-B knockout mice, Jk(a–b–) individuals have urine concentrating ability reduced by about one third [115,116]. This may be because other urea transporters, especially UT-A, compensate for the absence of UT-B in the kidney, and because maximal urea concentrating ability is rarely required under normal conditions. One-year old UT-B knockout mice, however, have severe renal dysfunction and structural damage, probably because of long-term hydronephrosis and polyuria [117].

Genome-wide association studies reveal an association between SNPs in *SLC14A1* and bladder cancer, identifying *SLC14A1* as a potential susceptibility gene [118,119].

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