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The Kidd (JK) Blood Group System

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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.

Contents

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

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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

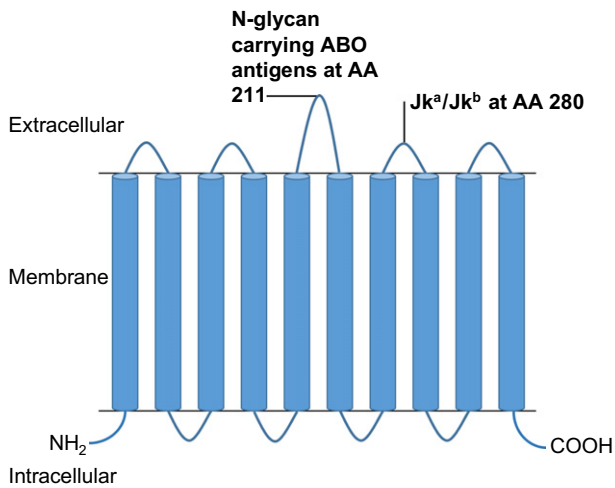

Figure. *JK* glycoprotein composed of 389 amino acids.