CHAPTER 15

Other protein blood groups

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Of the 35 currently known blood group systems, seven are carbohydrate in nature and are discussed in Chapter 13. Antigens of the remaining 28 blood group systems are carried by (glyco)proteins. Three of these 28 systems—Rh (ISBT 004), RhAG (ISBT 030), and the closely associated LW (ISBT 016)—are discussed in detail in Chapter 14. The remaining blood group systems are summarized in Table 15.1 and will be discussed here.

Many of the proteins carrying blood group antigens are functionally important; however, antibodies in only a few blood group systems represent a problem for the transfusion service, in that they may cause decreased survival/hemolysis of transfused antigen-positive red blood cells (RBCs) in patients with the antibody, or hemolytic disease of the fetus and newborn (HDFN) in a mother with antibodies directed at paternally inherited antigens on her baby’s erythrocytes. In addition, the presence of such antibodies may delay availability of compatible units of RBCs for transfusion and, occasionally, may make transfusion of incompatible RBCs unavoidable, particularly in urgent settings or with antibodies to high-incidence antigens. This chapter addresses only those antigens that elicit formation of clinically significant antibodies and briefly comments on the other blood group systems. Further details may be found in review articles and comprehensive textbooks.

MNS blood group system (ISBT 002)

Structure and function of glycoporphins A and B

Antigens of the MNS blood group system are carried by glycoporphin A (GPA) and glycoporphin B (GPB). Both molecules are present in a very high copy number in the plasma membrane: 0.5–1.0 × 10⁶ copies of GPA and 1–3 × 10⁵ molecules of GPB. GPA and GPB are encoded by homologous genes at chromosome 4q28-q31 that undoubtedly arose by gene duplication. Both glycoproteins are integral membrane proteins with a single transmembrane α-helical segment and with the N-termini located extracellularly (Figure 15.3). GPA was the first protein whose primary structure was determined by amino acid sequencing.

GPA carries the M and N antigens at its N-terminus. Although two amino acid substitutions underlie antigen specificity, an important requirement for recognition of these antigens by human antibodies is the presence of O-glycans attached to terminal serine and threonine residues.

GPB is homologous with GPA. Although the genes are greater than 95% identical, GYPB encodes a shorter protein because a point mutation at the 5′ splicing site of the third intron prevents incorporation of exon 3 into the translated mRNA. Because GYPB arose by duplication of the N allele of GYPA, GYPB+N, and the first 26 amino acids of GPB are therefore identical to those of GPA with N specificity, GPB expresses an N-like antigen designated as N (Figure 15.1).

The S and s isoforms of GPB differ at amino acid position 48. The S allele encodes methionine and the s allele, threonine. GPB also carries the U antigen whose epitope is adjacent to the point where GPB enters into the lipid bilayer (Figure 15.1), although the molecular basis of this antigen is not known.

As is frequently the case with genes arising by duplication and located next to each other, unequal crossing over or gene conversion may easily occur. Consequently, numerous hybrid molecules containing portions of GPA and GPB have been described. This phenomenon is responsible for many low-prevalence MNS antigens, which are carried by different hybrid proteins such as Mi+, V−, Hi+, MUT, MINY, St+, and DANE. GPA associates in the red cell membrane with the band 3 protein (SLC4A1). The epitope of the Wr° antigen from the Diego blood group system (see below) is formed by the association of GPA with band 3. This clearly demonstrates the intimate association of GPA and band 3 in the plasma membrane.

MNS in transfusion medicine

The most commonly encountered antibodies are directed against the M, N, S, and s antigens. Anti-M is a common antibody and may be found in the sera of persons who have not been exposed to human erythrocytes. M antibodies are predominately IgM with a thermal optimum below 30 °C; however, they frequently contain an IgG component, and occasionally are exclusively IgG. Nevertheless, anti-M is rarely clinically significant, and those examples of hemolytic anti-M are usually IgG and react at 37 °C. Selection of blood for transfusion can be made based on a negative cross-match irrespective of M antigen status. Similarly, anti-M is not considered to be an important antibody with regard to HDFN, although rare cases have been described. Anti-N is rare, most likely because of the immune tolerance induced by the N antigen on GPB, and is usually a weak, cold-reactive antibody of no clinical significance. These should be distinguished from the strong and potentially clinically
significant antibodies observed in persons of the rare phenotype M+N−S−U− who do not express GPB (hence N), and for whom phenotypically similar, cross-match-compatible blood should be provided.

In contrast to anti-M and anti-N, antibodies to S, s, and U usually occur after exposure to allogeneic erythrocytes, and all should be considered to be clinically significant because all are capable of causing hemolytic transfusion reactions (HTRs) and HDFN. The appropriate antigen-negative, cross-match-compatible blood should be selected for transfusion.

Lastly, severe HDFN due to rare antibodies to low-prevalence MNS antigens has also been reported and should be suspected in a strongly DAT-positive or symptomatic newborn where alloantibodies cannot be detected by routine screening.

### Table 15.1 Overview of the protein blood group systems other than Rh, RhAG, and LW

<table>
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<tr>
<th>ISBT Number</th>
<th>System Name</th>
<th>Gene Name ISBT</th>
<th>Gene Name HGNC</th>
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ISBT, International Society of Blood Transfusion; HGNC, Human Gene Nomenclature Committee.

Figure 15.1 Antigens of the Diego and MNS blood group systems in a scheme of band 3 and of glycophorins A and B. The membrane domain of band 3 with 14 transmembrane segments is shown. Mutations underlying the Diego blood group antigens are located in the putative first, second, third, fourth, and seventh extracellular loops. Positions of the M and N antigens in GPA and of the ‘N’, S, s, and U antigens in GPB are indicated. Arrows point to the sites in band 3 and GPA that are involved in formation of the W r a/epitope and, therefore, have to come into close contact in the membrane.
Lutheran blood group system (ISBT 005)

Lutheran antigens reside on B-CAM/LU (Figure 15.2), a pair of spliceosomes (protein products arising from the same gene because of alternative splicing of hnRNA) that belong to the immunoglobulin superfamily (IgSF). Basal cell adhesion molecule (B-CAM) is involved in adhesion of the basal surface of epithelial cells to the basement membrane. B-CAM/LU is a receptor for laminin. Expression of B-CAM/LU is increased on erythrocytes from patients with sickle cell disease and on a number of malignant epithelial tumors, which also lose the polarity of B-CAM/LU expression found in normal tissues.

The Lutheran blood group system contains multiple antigens; however, clinically significant antibodies are rarely encountered. The most important antigens are Lu and Lub. The prevalence of Lua is less than 10% in most populations, whereas Lu is a high-prevalence antigen with an average occurrence of 99.8% in all populations. Lutheran antigens are poorly developed at birth, and not surprisingly, anti-Lu has been associated only rarely with mild cases of HDFN. It does not cause transfusion reactions. Lu is somewhat more immunogenic, and anti-Lu has caused mild or moderate HTRs and mild HDFN. Of historical note, Lu and Se antigens, and anemia. Interestingly, only P1 blood group antigen expression was decreased in addition to Lu antigens; however, the proband was thrombocytopenic, and macrothrombocytopenia were observed.

Kell and Kx blood group systems (ISBT 006 and 019)

Structure, function, and interaction of the Kell and XK proteins

Antigens of the Kell blood group system are carried by a 93-kD red cell membrane glycoprotein, which consists of a short cytoplasmic N-terminal portion, a single membrane-spanning α-helical segment, and a large, 665-amino-acid extracellular C-terminal portion held in a globular conformation by multiple disulfide bonds (Figure 15.3). Kell antigens are inactivated by reducing agents such as dithiothreitol, suggesting that disulfide bonds are important in maintaining its antigenic conformation.

The Kell glycoprotein is a member of the neprilysin (M13) family of zinc metalloproteases. This family consists of Kell, neutral endopeptidase 24.11, two different endothelin-converting enzymes, the product of the PEX gene, and XCE. Members of the M13 subfamily of membrane zinc endopeptidases have widely different roles, including processing of opioid peptides, Met- and Leu-enkephalin, oxytocin, bradykinin, angiotensin, endothelins, and parathyroid hormone. Kell protein has been shown to preferentially activate endothelin-3; however, the in vivo physiologic role of Kell protein is probably complex, because K0 (null) persons are apparently healthy.

Kell glycoprotein interacts in the erythrocyte membrane with the 37-kD protein XK, which plays an important role in the expression of Kell system antigens. In contrast to the Kell protein, XK is a multiple membrane-spanning protein with both of its N- and C-termini located intracellularly (Figure 15.3). The function of XK is not known; however, absence of XK results in McLeod neuroacanthocytosis syndrome, an X-linked, late-onset neuromuscular disorder. Structurally, XK resembles the glutamate transporters, but it has very little amino acid sequence homology with this group of transport proteins. The Kell and XK proteins are covalently associated in the membrane by a disulfide link between cysteine 72 of Kell and cysteine 347 of XK (Figure 15.3). The gene encoding the Kx antigen is located on the short arm of the X chromosome near the loci for X-linked chronic granulomatous disease (CGD) and Duchenne muscular dystrophy (DMD).

Kell in transfusion medicine

The Kell blood group system is the second most important protein blood group system in transfusion medicine after Rh, because the antibodies can cause HTRs and HDFN. The most important antigens in this system are K (KEL1) and the antithetical k (KEL2). K and k are codominant autosomal alleles; and, although approximately 9% of whites and 2% of blacks are K-positive (i.e., K+k− or K+k+), the majority are K-negative (i.e., K−k+). Antigens of the Kell blood group system are highly immunogenic and, excluding ABO, K is second only to RhD in its potential to elicit production of alloantibodies.
K antigen, genotyping from amniocentesis or cell-free fetal DNA (cfDNA) in the mother’s plasma can be performed using molecular techniques.

**Null phenotypes**

There are two rare but clinically interesting null phenotypes. Rare individuals have erythrocytes that completely lack the Kell glycoprotein. Although these cells exhibit the null phenotype (K0), they are morphologically normal and survive normally in vivo. In contrast, individuals lacking the XK protein, and thus Kx antigen, exhibit depressed levels of the Kell glycoprotein.22 This phenotype, known as the McLeod neuroacanthocytosis syndrome, is associated with acanthocytic erythrocytes and a mild chronic hemolytic anemia.25 It is associated with late onset of neuromuscular symptoms that include muscle weakness or atrophy, cognitive alterations, and psychiatric symptoms. Association of the McLeod phenotype with other rare syndromes, most frequently with CGD and DMD or Becker muscular dystrophy (BMD), is caused by large gene deletions encompassing XK together with adjacent gene CYBB that encodes a large subunit of cytochrome b558 and is associated with X-linked CGD, and DMD that encodes dystrophin.33

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**Figure 15.3** Schematic representation of the Kell/XK complex in the red cell membrane. The XK protein is a multpass membrane protein, while Kell has only one transmembrane domain, most of which is exposed on the extracellular side. Due to multiple disulﬁde bonds, the extracellular portion of Kell is a globular structure; however, it is represented here schematically so that the positions of the main antigens can be shown. A disulﬁde bond between Cys572 of Kell and Cys347 of XK connects the two proteins. The position of the pantemeric sequence HELLLH is shown. Sequences HEXXH are involved in zinc binding and catalytic activity of zinc endopeptidases. The K/k polymorphism at amino acid 193 changes the consensus sequence for N-glycosylation at Asn191, which is not glycosylated in K. This difference in glycosylation may be important for the marked antigenicity of K. Positions of two additional sets of antithetical antigens Kp/a/Kp/b and Js/a/Js/b at amino acids 281 and 597 are indicated.

Anti-K is commonly found. Fortunately, because more than 90% of donor units are K negative, it is easy to obtain blood for transfusion to individuals with anti-K. In contrast, although anti-K is relatively rare, it is also of clinical significance and only 1 in 500 random donor units is antigen-negative. The other two sets of antithetical antigens to which antibodies are often found are Kp/a/Kp/b and Js/a/Js/b (Figure 15.3), although there are many other rare polymorphisms.

Mothers with anti-K are relatively rare, but since the introduction of Rh prophylaxis, anti-K accounts for nearly 10% of cases of severe HDFN. In contrast to RhD, anti-K titers are not good predictors of donor units are K negative, it is easy to obtain blood for transfusion to individuals with anti-K. In contrast, although anti-K is relatively rare, it is also of clinical significance and only 1 in 500 random donor units is antigen-negative. The other two sets of antithetical antigens to which antibodies are often found are Kp/a/Kp/b and Js/a/Js/b (Figure 15.3), although there are many other rare polymorphisms.

Mothers with anti-K are relatively rare, but since the introduction of Rh prophylaxis, anti-K accounts for nearly 10% of cases of severe HDFN. In contrast to RhD, anti-K titers are not good predictors of fetal anemia. In addition, affected Kell-alloimmunized infants have lower reticulocyte counts and amniotic fluid bilirubin concentrations than RhD-sensitized infants. Because Kell glycoprotein is synthesized early in erythropoiesis, anti-K has been hypothesized to suppress erythropoiesis at the progenitor cell level.18 In rare cases, administration of recombinant erythropoietin (rHuEPO) to the newborn has been tried with some success in cases where the mother has a Kell blood group system antibody causing prolonged anemia in a newborn whose RBCs and their progenitors express the cognate antigen in question.31,32

It is important to determine if a fetus is at risk when the mother has anti-K. The putative father should be typed and if he carries the
native West Africans are Fy(a–b–). This is most likely caused by the genetic adaptation for resistance to P. vivax malaria. However, it is not clear why this genetic advantage would lead almost to fixation of the Fy(a–b–) phenotype in the indigenous population of West Africa. In contrast to the other malarial parasites, P. vivax causes a relatively mild form of malaria. P. vivax causes a relatively mild form of malaria. Furthermore, despite the high prevalence of Duffy-negative individuals in West Africa, the Duffy protein has recently been shown to be a co-factor in platelet factor 4 (PF4)-dependent killing of P. falciparum parasites, suggesting that it has a protective role in this disease.38

A long-standing conundrum of immunohematology has been the well-known fact that transfused Fy(a–b–) people of African ancestry never develop anti-Fyb. This mystery was solved by the characterization of the mutation causing the Fy(a–b–) phenotype in native West Africans. The underlying mutation is a T → C substitution in the GATA site of the promoter region.39 This substitution prevents binding of the erythroid transcription factor GATA1 and abolishes transcription of the gene in the erythroid cells, while leaving the transcription of the FY gene in other tissues unaffected. Because the mutation occurred in the FY*B allele, the FYB antigen remains expressed in certain endothelial, epithelial, and brain cells, and, consequently, the transfusion recipient does not form antibodies against FYB. The GATA-1 mutation has been found on the FY*A allele in individuals from Papua New Guinea.40

FYb antibodies are found relatively frequently, constituting 6–10% of the clinically significant antibodies identified by immunohematology laboratories. For reasons not well understood, FYb is a relatively poor immunogen and, consequently, anti-Fyb is considerably less common. Both immediate and delayed HTRs caused by FYb incompatibility have been described, ranging from mild to severe hemolysis. HDFN is usually mild; only a few cases of severe HDFN have been reported. In contrast, anti-Fyb is associated only rarely with cases of mild HDFN and is usually found in delayed HTRs, although on rare occasions it has caused severe acute hemolysis.

**Kidd blood group system (ISBT 009)**

Kidd is an integral protein with 10 transmembrane domains and both N- and C-termini located intracellularly (Figure 15.4). Of the five extracellular loops, the longest, third loop is N-glycosylated, and the relatively short fourth loop carries an Asp280Asn polymorphism corresponding to the Jka/Jkb antigens. Kidd protein is expressed not only on the red cell surface but also on neutrophils and in the kidney.

The two main antigens of the Kidd blood group system, Jka and Jkb, are found with almost identical frequencies in white populations. Jka is a better immunogen, and anti-Jka is found more frequently than anti-Jkb. Anti-Jkb may cause severe immediate or delayed HTRs and, occasionally, HDFN. It is one of the most dangerous immune antibodies because of its tendency to decrease to undetectable levels in between transfusions and its relatively low affinity for Jk(a+) erythrocytes. For these reasons, it accounts for a large proportion of delayed HTRs. Anti-Jkb may also cause immediate or delayed HTRs, albeit less severe than those caused by anti-Jka (see http://www.shotuk.org/shot-reports/ for more information). Several cases of mild HDFN caused by anti-Jkb have been reported.

The finding that cells of the Jk(a–b–) phenotype are resistant to lysis by 2M urea led to the discovery of the function of the glycoprotein carrying the Kidd antigens. Based on this finding and on in vitro expression of the cloned Kidd cDNA, it is now known that the protein is the primary erythrocyte urea transporter (SLC14A1), although the importance of urea transport for red blood cells is not completely understood. Its presence or absence may not be critical for red cell structure and function, because carriers of the Jk(a–b–) phenotype have erythrocytes indistinguishable from those of controls. While individuals with the Jk(null) phenotype lack SLC14A1 completely, weakly expressed forms of the protein have been found, in which the Jka and/or Jkb antigens may be barely detectable.45–47

**Diego blood group system (ISBT 010)**

Antigens of the Diego blood group system are carried by band 3 (SLC4A1, anion exchanger 1), the most abundant integral protein of the red cell membrane together with GPA (see above). Band 3 is also one of the most important proteins for the structure and function of the membrane because it maintains red cell integrity by linking the red cell membrane to the underlying spectrin-based membrane skeleton. It also mediates exchange of chloride and bicarbonate anions across the plasma membrane, thereby significantly increasing the carrying capacity of blood for carbon dioxide.
Band 3 consists of a cytoplasmic and a membrane domain. The membrane domain contains 14 transmembrane helices connected by ecto- and endoplasmic loops (Figure 15.1). The fourth loop of band 3 is N-glycosylated, and the attached carbohydrate chain carries over half of the red cell ABO blood group epitopes. Several disorders of red cell structure and function have been associated with mutations in the band 3 gene, including Southeast Asian ovalocytosis, autosomal dominant spherocytosis, and distal renal tubular acidosis.

Despite being the most abundant protein of the red cell membrane, it was only in 1992 that Spring et al. reported that the Memphis II variant of erythroid band 3 protein carries the Diα blood group antigen. Diα was originally described in South American Indians by Layrisse et al. in 1955. The antithetical antigen Diβ was reported by Thompson et al. in 1967. Diα and Diβ represent co-dominantly expressed gene products. Diα is a low-prevalence blood group antigen in persons of European ancestry who carry the antithetical high-prevalence antigen Diβ. Prevalence of Diα is as high as 8% in certain areas of Southeast Asia and reaches up to 40% in some groups of South American Indians. Diα was used as one of the original markers for studying migration of people from Southeast Asia across the Bering Strait and southward through the American continents. Cloning and sequencing of SLC4A1 identified the substitution 854 Pro→Leu in the last extracellular loop of band 3 as the molecular basis of the Diα antigen. Diβ corresponds to the wild-type band 3 with proline in position 854.

Subsequently, the low-prevalence blood group antigen Wrα was mapped to the fourth extracellular loop. The antithetical Wrβ antigen is observed only when both GPA and band 3 protein are expressed in the erythrocyte membrane; thus, erythrocytes that lack GPA (so-called En(a−) phenotype) but have normal band 3 are also Wr(b−) (Figure 15.1). Numerous additional low-prevalence antigens are associated with single point mutations on band 3 and included in the Diego system. Positions of the amino acid polymorphisms in the band 3 molecule are shown in Figure 15.1, which also indicates the regions of band 3 and GPA that interact in the membrane and are involved in formation of the Wrβ antigen.

Some antigens of the Diego blood group system have been localized to the regions of band 3 protein that have been implicated in the adhesion of abnormal erythrocytes, such as sickle cells or malaria-infected erythrocytes, to vascular endothelium. Erythrocytes from carriers of low-prevalence blood group antigens in band 3 may serve as a model for evaluation of the sequence requirements for adhesion. The so-called senescent or aging red cell antigen may also be located in the extracellular loops of band 3.

### Xg blood group system (ISBT 012)

The Xg system contains two antigens, Xgα and CD99, carried by glycoproteins of 180 and 185 amino acids, respectively. The function of Xg glycoprotein in erythrocytes is not known, although it is 48% homologous to CD99, an adhesion molecule. Xgα was described in 1962 as the first sex-linked blood group antigen, and the antigen-positive incidence was shown to be significantly different in men (62%) than women (89%). The XG gene is located in the pseudoautosomal region of the X chromosome, and consequently escapes lyonization (X-inactivation). Xgα antibodies are clinically insignificant.

### Scianna blood group system (ISBT 013)

The seven antigens of the Scianna blood group system are carried by the erythrocyte membrane-associated protein (ERMAP), potentially a receptor/signal transduction molecule specific for erythroid cells. Mild HDFN and mild posttransfusion hemolysis caused by anti-Sc-2 and anti-Sc-3 antibodies have been reported.

### Colton and GIL blood group systems (ISBT 015 and 029)

Antigens of these two blood group systems are carried by members of the large aquaporin family. Antibodies against the two antigens of the Colton blood group system, the high-prevalence Coα and the less common, antithetical Coβ, are rare and have only rarely been associated with mild HTRs and mild HDFN. These two antigens, together with the high-prevalence Co3 and Co4 antigens present on all erythrocytes except those of the very rare null phenotype Co(a−b−), are carried by aquaporin-1 (AQP1), a member of a large family of water channels. It is present in the membrane as a tetramer. Expression of AQP1 in Xenopus oocytes is associated with dramatic swelling and lysis of the cell; however, the Co(a−b−) phenotype is associated with only slightly abnormal erythrocytes and with normal kidney function despite the fact that AQP1 is the major water channel of human kidney. The GIL antigen is carried by aquaporin-3 (AQP3), which differs from AQP1 in that it transports glycerol, water, and urea.

### Chido/Rodgers blood group system (ISBT 017)

Antigens of the Chido/Rodgers blood group system are the only protein antigens that are not produced by erythrocytes but instead adhere to the red cell surface (Lewis antigens are glycolipids). They are carried by the complement component C4. Although antibodies against the nine known antigens of the system are generally benign, a severe anaphylactic reaction following a transfusion of platelets to a patient with anti-Ch3 has been described.

### Gerbich blood group system (ISBT 020)

As in the MNS system, antigens of the Gerbich system are located on glycoporphins C and D (GPC, GPD). The glycophorin terminology is in fact the only common feature of these two classes of glycoporphins. There is otherwise no homology between the Gerbich and MNS genes. GPC and GPD are the products of a single gene, GYP, and are the products of alternative splicing. GPC is produced by a full-length gene transcript, whereas the less abundant GPD is produced from a second initiation methionine that encodes a protein that is 21 amino acids shorter. Although present in much smaller copy numbers than GPA and GPB, GPC plays an important role in the structural integrity of the red cell membrane. In the Leach phenotype, deletions of exons 3 and 4 or a frameshift mutation leads to complete absence of glycoporphins C and D from the plasma membrane. The affected individuals have moderate elliptocytosis and decreased red cell deformability and mechanical stability. Antibodies in the Gerbich system, to both the high- and low-prevalence antigens, are rare and, in the vast majority of cases, clinically insignificant.
Knops blood group system (ISBT 022)
Antigens are located on the C3b/C4b complement receptor 1 (CR1, CD35). CR1 protects erythrocytes from autohemolysis by inhibiting the classical and alternative complement pathways through cleavage of C4b and C3b. CR1 is a large 190- to 280-kD molecule. It contains 30 complement control protein domains (CCPDs) of about 60 amino acids. Seven CCPDs form a long homologous repeat (LHR) of about 450 amino acids. Various forms of CR1 contain up to six LHRs.79 Erythrocyte CR1 binds immune complexes and carries them to the liver and spleen for removal. Expression of CR1 on erythrocytes varies widely from 20 to 1500 molecules and is decreased in hemolytic anemias, AIDS, systemic lupus erythematosus, and other autoimmune disorders. Plasmodium falciparum–infected erythrocytes deficient in CR1 have greatly reduced rosetting capacity, indicating an essential role for CR1 in rosette formation and raising the possibility that CR1 polymorphisms in Africans that influence the interaction between erythrocytes and parasite-encoded protein PfEMP1 may protect against severe malaria.77 CR1 could therefore be a potential target for future therapeutic interventions to treat severe malaria.

Indian blood group system (ISBT 023)
The four antigens of this system, Ina, Inb, INFI, and INJA, reside on CD44, an adhesion molecule expressed in leukocytes, fibroblasts, epithelial cells, and other tissues. CD44 is an important lymphocyte homing receptor (Figure 15.2). Transfection of nonadherent cell lines with CD44 cDNA confers an adherent phenotype.79 As with the Lutheran antigens, expression of Ina and Inb is suppressed by In (Lu). The high prevalence antigen, AnWj, is also associated with CD44 and is a receptor for Haemophilus influenzae.80 Antibodies to Indian blood group system antigens are rare and of limited clinical significance. Anti-AnWj is extremely rare.

Blood group antigens on glycosylphosphatidylinositol-linked proteins: Cartwright (ISBT 011), Dombrock (ISBT 014), Cromer (ISBT 021), JMH (ISBT 026), and CD59 (ISBT 035)
The common denominator of antigens in these blood group systems is the linkage of the carrier protein to the glycosylphosphatidylinositol (GPI) anchor (Figure 15.5). The Cartwright (Yt) blood group system consists of two antigens, Yta and Ytb, which are located on red cell acetylcholinesterase. The function of acetylcholinesterase on erythrocytes is not understood, although it appears to play a role in vascular signaling.81 Most examples of anti-Yta are benign.

The eight antigens of the Dombrock system are located on ART-4, a member of the adenosine 5’-diphosphate (ADP)-ribosyltransferase ectoenzyme gene family.82 Dombrock expression is developmentally regulated during erythroid differentiation and occurs at highest levels in the fetal liver. Doa and Dob antigens differ in a single amino acid substitution within the RGD motif of the molecule.83

The Cromer blood group system contains 18 antigens located on decay-accelerating factor (DAF, CD55), a complement regulatory protein. Extraordinarily, much of the polymorphism appears restricted to one ethnic group or another, making it a very interesting blood group system.84 Antibodies to Cromer blood group antigens are of limited clinical importance, and due to the expression of DAF on the placenta, antibodies disappear over the course of pregnancy and pose no threat to the fetus.85 Although DAF was the first complement regulatory protein identified, it plays only a minor role in complement-mediated lysis, the more important being CD59 (MIRL). This was clearly demonstrated in the case of the null phenotype, Inab, which is associated with lack of DAF expression on all circulating cells but not with increased hemolysis.86

The six high-prevalence antigens of the JMH blood group system reside on a GPI-linked protein, semaphorin 7A (CD108), which is part of a plasma membrane complex associated with intracellular protein kinases.87 CD108 is expressed in multiple tissues and may play a role in signal transduction. Anti-JMH is generally a weak, clinically benign antibody found in older people.

CD59 was recently assigned blood group system status following the report of an antibody produced in response to transfusion in a CD59-deficient girl.88 The clinical significance of the antibody is not known, although the absence of CD59 in this and other patients has severe clinical consequences.

Antibodies in these blood group systems have been associated only occasionally with mild HTRs or HDFN. Not surprisingly, expression of all GPI-linked antigens is decreased in paroxysmal nocturnal hemoglobinuria (PNH), a multisymptomatic disorder caused by defects in the X-linked phosphatidylinositol glycan class A (PIG-A) gene, which participates in an early step of GPI anchor synthesis.89 The pathophysiology of PNH is due almost exclusively to the absence of CD55 and CD59, which are important regulators of the complement system: CD55 accelerates the rate of destruction of membrane-bound C3 convertase and thus limits C3 activation; and CD59 reduces the amount of the membrane attack complex (MAC) formed by preventing C9 accumulating and thus lytic pore formation. Anemia, due to both hemolysis and bone marrow

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Chapter 15: Other protein blood groups
failure, and thrombosis are also common in PNH patients. See Chapter 12 for a complete discussion of PNH.

**Other minor blood group systems: OK (ISBT 024), RAPH (ISBT 025), JR (ISBT 032), LAN (ISBT 033), and VEL (ISBT 034)**

The three high-prevalence antigens of the OK blood group system are carried on basigin (CD147), a widely distributed IgSF molecule. Rare Ok(a–) individuals have so far been reported only in Japan, and absence of the high-prevalence antigens OK2 and OK3 has been described in single families. As with LW, its extracellular domain contains two immunoglobulin domains. The function of the Ok glycoprotein in erythrocytes is not known, but it has recently been described as a novel receptor of *P. falciparum*.92

MER2 is the only antigen of the RAPH system carried on CD151. CD151 is a tetraspannin that is expressed not only on erythrocytes but also on basement membranes, where in the kidney and in skin it is thought to facilitate binding of integrins to the extracellular matrix to maintain integrity.93

Two proteins in the ABC transporter family were recently found to carry blood group antigens and thus solved the molecular whereabouts of two previously uncharacterized high-prevalence antigens. The Jr(a–) phenotype was localized to ABCG2, where the Jr phenotype represented the null phenotype.94,95 ABCG2 is a well-characterized protein that confers multidrug resistance (e.g., in breast cancer), and is also important in porphyrin homeostasis. It has a high affinity for urate, and Japanese Jr(a–) individuals have a higher incidence of gout. Anti-Jr is not usually considered clinically important; however, it has caused severe HDFN.96

The high-prevalence Lan antigen is carried on ABCB6, a mitochondrial porphyrin transporter considered essential for heme synthesis. Like Jr(a–), Lan– individuals represent the null phenotype and lack the protein. ABCB6 is highly expressed during erythropoiesis. Anti-Lan is not generally considered clinically important, and antigen expression is variable.98

Expression of the clinically important Vel antigen has been shown to be dependent on SMIM1, a small transmembrane protein of unknown function.99–101 Intriguingly, the protein is well-conserved across species, suggesting that it is an important protein, and GWA studies suggest that it might play a role in iron metabolism.102 Anti-Vel is considered clinically significant and has caused severe hemolytic transfusion reactions.

**Summary**

The century-long history of modern transfusion medicine and immunohematology practice led to the characterization of an enormous number of blood group antigens with often confusing terminology. These antigens have been arranged into a complex framework of blood group systems, collections, and low- and high-prevalence antigens.103 Advances in biochemical and molecular biology techniques in the past two decades led to a detailed structural characterization of most proteins carrying blood group antigens and to a better understanding of the relation between gene variations, amino acid polymorphisms, protein structure, and immunogenicity of individual antigens. Better understanding of the molecular biology, biochemistry, and immunogenicity of proteins carrying blood group antigens will undoubtedly contribute to accurate compatibility testing and to safe transfusion of erythrocytes.

**Disclaimer**

The author has disclosed no conflicts of interest.

**Key references**

A full reference list for this chapter is available at: [http://www.wiley.com/go/simon/transfusion](http://www.wiley.com/go/simon/transfusion)


