Clinical significance of antibodies to antigens in the Raph, John Milton Hagen, I, Globoside, Gill, Rh-associated glycoprotein, FORS, JR, LAN, Vel, CD59, and Augustine blood group systems

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This article reviews information on the clinical significance of antibodies to antigens in the Raph, John Milton Hagen, I, Globoside, Gill, Rh-associated glycoprotein, FORS, JR, LAN, Vel, CD59, and Augustine blood group systems. Antibodies to many of the antigens in these groups are rarely encountered because of the high prevalence of the associated antigens in most populations. For many of these antibodies, the clinical significance—that is, the potential to cause reduced survival of transfused antigen-positive red blood cells or a transfusion reaction (e.g., anti-P, anti-Jr, and anti-Lan), and/or hemolytic disease of the fetus and newborn (e.g., anti-RHAG4 and anti-Vel)—has been documented. For other antibodies, their prevalence is so rare that information on the clinical significance of their antibodies is not available (e.g., anti-FORS1).

Key Words: clinical significance, antibodies to red blood cell antigens, Raph, John Milton Hagen, I, Globoside, Gill, Rh-associated glycoprotein, FORS, JR, LAN, Vel, CD59, Augustine

Raph Blood Group System

The Raph blood group system contains just one antigen, MER2 (RAPH1), located on the tetraspanin CD151 glycoprotein (TM4SF). The true MER2− phenotype, associated with the presence of anti-MER2, is very rare and results from mutations in CD151, but there is a quantitative red blood cell (RBC) polymorphism in which RBCs of about 8 percent of white individuals are serologically MER2−.

Clinical Significance

There have been six reports of human alloantibodies to MER2. Three of the subjects were found to have a stop codon in the CD151 gene, which encodes a member of the tetraspanin family of proteins. These three individuals had nephropathy and deafness, and two of the three, who were siblings, also had skin lesions, deafness, and β-thalassemia minor. The fourth subject had missense mutation c.533G>A (p.Arg178His). Subjects 5 and 6 shared missense mutation c.511C>T (p.Arg171Cys) as well as a synonymous single-nucleotide mutation (c.579A>G) and had no clinical features. Although the CD151 protein is critical to cell adhesion and signaling and is implicated in cancer progression, its significance in transfusion medicine is limited to only one report of a hemolytic transfusion reaction (HTR). Least-incompatible RBC units should be selected for transfusion to patients with anti-MER2. No information on anti-MER2 causing hemolytic disease of the fetus and newborn (HDFN) is available.

John Milton Hagen Blood Group System

The John Milton Hagen (JMH) blood group system consists of six high-prevalence antigens that are recognized by the International Society of Blood Transfusion (ISBT) and are numbered sequentially from JMH1 through JMH6. Confirmed JMH variants are named with the first letter from the antibody maker’s first name following JMH (JMH2 named JMHK, JMH3 named JMHL, JMH4 named JMHG, JMH5 named JMHM, JMH6 named JMHQ). These antigens are located on the Sema7A protein. The chromosomal location of SEMA7A is 15q22.3-q23. JMH1 is the primary antigen in the system and is present in greater than 99 percent of all individuals. The JMH1− phenotype is more commonly acquired by depression of the antigen. This finding might explain the serologic observation of a positive direct antiglobulin test (DAT) seen in many individuals with anti-JMH.

Clinical Significance

JMH1, commonly known as JMH, is most notable because transient depression of the antigen occurs, and (auto)anti-JMH may develop. JMH− patients with anti-JMH often have no history of transfusion or pregnancy. Of seven JMH antibodies,
five were IgG4 and two were IgG1, although IgG3 anti-JMH has been described. There are numerous cases where patients with anti-JMH have been transfused with JMH+ blood with no adverse effects. One such patient received 20 units of JMH+ blood in 10 months, with the expected hemoglobin rise. There are no reports of JMH antibodies causing HDFN, which is unsurprising considering that JMH antigens are expressed very weakly on cord cells. One patient with anti-JMH is reported to have experienced an acute intravascular HTR, but evidence that the JMH antibody was responsible is limited. Antibodies developed in the rare JMH variant types may cause reduced RBC survival.

Clinical Significance

Potent cold reactive antibodies responsible for cold agglutinin disease are usually of I specificity. These antibodies are generally monoclonal and are usually IgM, but IgG autoanti-I can also occur. They directly agglutinate I+ RBCs at 4°C with varying thermal amplitude but are generally inactive above 30°C. One autoanti-I active at 30°C caused an acute HTR in a small child when 2 units of blood were transfused immediately after removal from the refrigerator. Transient, polyclonal, or oligoclonal autoanti-I may arise from infection, most typically by *Mycoplasma pneumoniae*.

Alloanti-I of high titer is rare and usually presents in the sera of i adults. These antibodies are almost invariably IgM and are active only at low temperatures. Rare examples may be hemolytic and have a thermal range up to 37°C, and some anti-I with a thermal range below 37°C can cause shortened survival of transfused I+ RBCs. One anti-I became potentially clinically significant after transfusion of 6 units of I+ blood.

### Globoside Blood Group System

The P blood group antigen of the Globoside system is a glycolipid structure, also known as globoside, on the RBCs of almost all individuals worldwide. The P antigen (Gb4) is intimately related to the Pk and NOR (P1PK4) antigens.

The molecular genetic basis of globoside deficiency is the absence of functional P synthase caused by mutations at the *B3GALNT1* locus. Other related glycolipid structures, the LKE and PX2 antigens, remain in the Globoside blood group collection pending further evidence concerning the genes and gene products responsible for their synthesis.

### Clinical Significance

Anti-P is found in the serum of all Pk individuals and can be separated from serum of p individuals by adsorption with P1k or P2k cells or by inhibition with hydatid cyst fluid. When complement is present, anti-P will hemolyze P1 or P2 phenotype RBCs. P antibodies are IgM and often also IgG, are usually reactive at 37°C, and can cause severe intravascular HTRs. Autoanti-P is associated with paroxysmal cold hemoglobinuria. P antigen is also a receptor of parvovirus B19.

Cytotoxic IgM and IgG3 antibodies directed against P or Pk antigens are associated with a higher-than-normal rate of spontaneous abortion in women with the rare p, P1k, and P2k phenotypes.

### Gill Blood Group System

The Gill blood group system was added to the list of systems already recognized by the ISBT in 2002. GIL, the only antigen of the Gill system, is an antigen of high prevalence located on the water and glycerol channel aquaporin-3 (AQP3). The GIL- phenotype results from homozygosity for a splice mutation in *AQP3*. Anti-GIL has been identified in five Gil- white women who had been pregnant at least twice.

### Clinical Significance

Five examples of anti-GIL have been identified, all in white women who had been pregnant at least twice. No GIL- individual was found by screening 23,251 white American and 2841 African American women with anti-GIL. RBCs from two
of the babies of mothers with anti-GIL gave a positive DAT, but there were no clinical symptoms of HDFN. Anti-GIL may have been responsible for an HTR, and results of monocyte monolayer assay (MMA) with two GIL antibodies suggested a potential to cause accelerated destruction of transfused GIL+ RBCs.\(^2\)

**The Rh-Associated Glycoprotein Blood Group System**

In 2010, the recognition that three RBC surface antigens were located on RhAG encoded by \(RHAG\) led to the establishment of a new blood group system. Two high-prevalence antigens, Duclos (RHAG1) and DSLK (RHAG3), two low-prevalence antigens, OI(a) and (RHAG2), and RHAG4, have serologic characteristics suggestive of expression on RhAG, but RHAG4 has been shown to not exist and is under investigation by ISBT to be retracted.\(^13\)

**Clinical Significance**

No data are available.\(^4\)

**FORS Blood Group System**

This blood group system has been named FORS after its original finder, Lund professor John Forssman. The FORS antigen (originally recognized as the \(A_{\text{pa}}\) phenotype) was discovered by weak reactivity of RBCs against polyclonal anti-A reagents, reactivity against the lectin *Helix pomatia* (snail anti-A), and no reactivity with the plant anti-A, lectin, *Dolichos biflorus*, in two different families. Genomic analysis of the ABO locus in both samples revealed that they were genetically group O, and the reactivity described must be due to other phenomena.\(^14,15\)

**Clinical Significance**

The clinical significance of anti-FORS1 is not known.\(^4\)

**JR Blood Group System**

The JR blood group system (ISBT 032) consists of one antigen, \(Jr^a\), which is highly prevalent in all populations (>99%). \(Jr^a\) is located on the ABCG2 transporter, a multipass membrane glycoprotein (also known as the breast cancer resistance protein [BCRP]), which is encoded by the \(ABCG2\) gene on chromosome 4q22.1.\(^16\) The rare \(Jr(a–)\) phenotype has been found mostly in Japanese and other Asian populations, but also in people of northern European ancestry, in Bedouin Arabs, and in one Mexican individual. The rare \(Jr(a–)\) phenotype mostly results from recessive inheritance of \(ABCG2\) null alleles caused by frameshift or nonsense changes.\(^17\) To date, more than 25 different mutations responsible for the absence of ABCG2 as well as mutations giving rise to weakened \(Jr^a\) expression have been identified.\(^16\)

**Clinical Significance**

ABCG2 expression levels in cord RBCs are higher than those in adult RBCs, and the change of ABCG2 expression in erythroid lineage cells may influence the clinical course of fetal anemia with anti-\(Jr^a\).\(^23\) Anti-\(Jr^a\) may be stimulated by transfusion or pregnancy and has been detected in untransfused \(Jr(a–)\) women during their first pregnancy.\(^24\) Most anti-\(Jr^a\) are IgG1 and sometimes IgG3. Anti-\(Jr^a\) may fix complement, can be a dangerous antibody in pregnancy, and has been implicated in severe and fatal HDFN; in other pregnancies with anti-\(Jr^a\), however, indications of HDFN have been no more than a positive DAT on cord cells or mild neonatal jaundice. Many transfusions of \(Jr(a+)\) RBCs to patients have resulted in no signs of hemolysis, although incompatible transfusion may cause a sharp rise in the titer of anti-\(Jr^a\), resulting in signs of an acute HTR in subsequent transfusions. A patient with anti-\(Jr^a\) developed rigors after transfusion of 150 mL crossmatch-incompatible blood. Least-incompatible RBC units may be suitable for transfusion to most patients with anti-\(Jr^a\), but \(Jr(a–)\) RBCs should be selected in cases where the anti-\(Jr^a\) is of high titer.\(^2\)

**LAN Blood Group System**

LAN (Langereis) was officially recognized by the ISBT in 2012 as the 33rd human blood group system. It consists of one high-prevalence antigen, Lan (LAN1).\(^25\) The \(ABCB6\) protein is the carrier of the Lan blood group antigen.\(^16,25\) The \(ABCB6\) gene (chromosome 2q36, 19 exons) encodes the \(ABCB6\) polypeptide, known as a porphyrin transporter. The exceptional Lan– individuals do not express \(ABCB6\) (Lan– phenotype) owing to several different frameshift and missense mutations.\(^25\) To date, more than 40 \(ABCB6\) alleles that encode Lan– or Lan+\(^w\) phenotypes have been described,\(^26\) and quantitation of Lan antigen in Lan+, Lan+\(^w\), and Lan– phenotypes have been performed.\(^27\) Despite the Lan antigen role in erythropoiesis and detoxification of cells, Lan– individuals do not appear to demonstrate susceptibility to any disease.
Clinical Significance

Anti-Lan has been reported in two African American individuals as well as in other populations including Caucasians and Asians and may be stimulated by transfusion or pregnancy. The original anti-Lan was responsible for an immediate HTR characterized by fever and chills. There is no report of naturally occurring alloanti-Lan; none of the Lan– siblings of the Lan– propositi have anti-Lan. Anti-Lan has been described as having variable clinical significance, either for HTRs (none to severe) or HDFN (none to mild). Lan alloantibodies are mostly IgG1 and IgG3, although IgG2 and IgG4 may also be present. Some anti-Lan fix complement; others do not.

Despite challenging conditions caused by the scarcity of Lan– donors worldwide, ideally Lan– RBCs should be selected for transfusion to patients with anti-Lan, especially individuals with a high-titer antibody, although least incompatible RBCs may be suitable for patients with weak examples of the antibody. The only autoanti-Lan was reported in a patient with mild autoimmune hemolytic anemia (AIHA) with depressed Lan antigen expression.

Vel Blood Group System

Vel is an RBC antigen that is expressed by more than 99.9 percent of the population. The recognition of Vel dates to 1952, when a patient, named Mrs. Vel, suffered a transfusion reaction due to the presence of an antibody that was found to agglutinate sera of over 10,000 individuals. The antibody was named anti-Vel.

Recently, the SMIM1 protein was shown to carry the Vel blood group antigen. Using a high-density single nucleotide polymorphism array, Storry et al. identified the SMIM1 gene residing in a 97-kb region of homozygosity on chromosome 1p36 in the vicinity of the RH locus. A frameshift deletion of 17 nucleotides in exon 3 of SMIM1 is responsible for the Vel– phenotype. Genotype screening estimated that ~1 in 17 Swedish blood donors is a heterozygous deletion carrier and ~1 in 1200 is a homozygous deletion knockout.

Absence of CD59 is associated with hemolytic anemia and with thrombosis as well as with other autoimmune diseases such as systemic lupus erythematosus.

Clinical Significance

No data are available.

Augustine Blood Group System

At is a high-prevalence antigen found on the RBCs of over 99 percent of individuals. The first literature referring to the At antibody, which can be responsible for severe HTRs and mild HDFN, dates to the 1960s. Applewhaite et al. identified an antibody with a novel specificity in the serum of Mrs. Augustine when the RBCs of her third child gave a positive DAT at birth. Her alloantibody, abbreviated as anti-At after
her name, reacted with more than 6600 blood donors tested at that time, indicating that At was a high-prevalence antigen. All anti-At producers reported thus far have been of African ancestry, like Mrs. Augustine.

Recently, it has been shown that SLC29A1 encoding the equilibrative nucleoside transporter 1 (ENT1) specifies a new candidate gene for a novel blood group system that includes the At antigen. Daniels et al. reported a nonsynonymous SNP in SLC29A1 (rs45458701) is responsible for the At(−) phenotype. Although all At(−)-reported propositi are of African ancestry with functional ENT1, they identified three siblings of European ancestry who were homozygous for a null mutation in SLC29A1 (c.589+1G>C) and thus have the Augustine null phenotype. These individuals lacking ENT1 exhibit periarticular and ectopic mineralization, which confirms an important role for ENT1/SLC29A1 in human bone homeostasis, cardioprotection, and drug transport in erythrocytes.

Clinical Significance

At antibodies are mostly IgG, but IgM could also be present and can directly agglutinate At(+) RBCs. Of two IgG anti-At, one was IgG1, and the other consisted of IgG1, IgG3, and IgG4. At antibodies facilitate rapid destruction of 51Cr-labeled At(+) RBCs in vivo and give positive results in the in vitro functional assay, the MMA. Ideally, At(−) RBCs should be selected for transfusion to patients with anti-At, although least incompatible RBC units may be suitable for patients with weak examples of the antibody.

One anti-At caused an immediate HTR with chills and nausea during an RBC survival study, and another caused a severe delayed HTR after transfusion of multiple units of At(+) RBCs. Despite numerous pregnancies involving anti-At, only one of the infants had moderately severe HDFN requiring phototherapy. In three At(−)-reported patients from the southern United States, the anti-At was concomitant with autoimmune disease.

References


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