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International Society of Blood Transfusion Working Party on red cell immunogenetics and blood group terminology: Cancun report (2012)

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Abstract

The International Society of Blood Transfusion Working Party on red cell immuno-genetics and blood group terminology convened during the International congress in Cancun, July 2012. This report details the newly identified antigens in existing blood group systems and presents three new blood group systems.

Keywords

blood groups; genetics; red blood cell; terminology

Introduction

The Working Party met in Cancun, Mexico during the 2012 International Society of Blood Transfusion (ISBT) Congress. As in previous meetings, matters pertaining to blood group antigen nomenclature were discussed.

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A total of 10 new blood group antigens were added to six of the current blood group systems (Table 1). In addition, three antigens were assigned to three new blood group systems (Table 2), one *de novo* (FORS) and two others (JR and Lan), that elevate the high-prevalence antigens Jr^a and Lan, respectively, from the 901 Series of High Incidence Antigens to system status. This brings the current total of recognized blood group antigens to 339, of which 297 are clustered within 33 blood groups systems and the remainder are accommodated in the Collections, 700 Series of Low Incidence Antigens or the 901 Series of High Incidence Antigens.

System 3: P1PK

A single nucleotide substitution (c.631C > G) in *A4GALT* has been shown by Suchanowska and colleagues [1] to be responsible for the synthesis of the NOR antigen. The acceptor specificity of the 4-α-galactosyltransferase is altered by the encoded p.Gln211Glu change, while the donor specificity appears to remain unchanged. Thus, in addition to utilizing lactosylceramide for P^k synthesis and paragloboside to make P1, this enzyme can also use globoside (P antigen) to synthesize NOR in the presence of the genetic alteration described above. NOR is a low-prevalence antigen that was first described in an American family as an inherited polyagglutinable characteristic [2]. Unlike other forms of polyagglutinable factors, NOR+ red blood cells (RBCs) are not agglutinated by the common plant lectins *Arachis hypogea*, *Glycine soja*, *Salvia sclarea*, *Salvia horminum* or *Bandereia simplicifolia* II, or by the snail lectin *Helix pomatia*. However, NOR+ RBCs are reactive with approximately 75% of ABO-compatible human sera, and this reactivity was completely inhibited by hydatid cyst fluid or by avian P1 blood group substance [2].

System 4: Rh

Two antigens have been added to the Rh system. RH60 (PARG) is a low-prevalence antigen, characterized by a single nucleotide change c.501G > A in *RHCE* exon 4 [3]. It is associated with an *RHCE*Ce* haplotype, and the substitution encodes a change of p.Met167Ile. RH61 (CEVF) is a new high-prevalence antigen that is lacking from the Rhce protein encoded by a rare *RHCE*ce* allele named *RHCE*ceMO* that carries the SNPs c.48G > C and c.667G > T [4]. The allele encodes a variant e antigen and an altered Rhce protein that lacks the discrete high-prevalence antigen CEVF, as demonstrated by the e-like antibody produced in patients homozygous for *RHCE*ceMO*, which is not compatible with $hr^B–$ or $hr^S–$ or Hr– or $Hr^B–$ erythrocytes.

System 6: Kell

Three new high-prevalence antigens have been identified in the Kell blood group system. These are KEL36 (KETI), KEL37 (KHUL) and KEL38 (KYOR), respectively.

The first of these, KETI, was found following the identification of an antibody to an apparent high-prevalence antigen in a 65-year-old man. The antibody was non-reactive with K_0 and KASH− RBCs only but otherwise had an unremarkable Kell blood group antigen phenotype [5]. Sequence analysis revealed homozygosity for a single nucleotide mutation, c.

1391C > T in exon 12, that encoded an amino change of p.Thr464Ile. Absence of KETI did not affect the expression of k, Kp^b, Js^b or K11 that were inherited on the same allele. In another study, Velliquette *et al.* [6] reported that some KETI− probands have weakened expression of K11.

KEL37 or KHUL was characterized by an antibody to a high-prevalence antigen in the plasma of an elderly woman of Asian descent. The patient's plasma did not react with K_0 RBCs nor, in the initial testing, with multiple examples of Kp(b−) RBCs, although her RBCs typed Kp(b+) [7]. Four years later, her plasma reacted with Kp(b−) RBCs but was still compatible with K_0 RBCs. Sequence analysis revealed homozygosity for the nucleotide transition c.877C > T in exon 8, both in the patient and in her crossmatch-compatible sister. The nucleotide change is predicted to encode p.Arg293Trp. Despite being adjacent to the amino acid position that defines the low-prevalence antigen KYO (p.Arg292Gln) [8], the patient's plasma reacted with KYO+ RBCs and those of the patient's compatible sister were non-reactive with anti-KYO, thus demonstrating that KHUL and KYO are independent.

Interestingly, the antithetical antigen to KYO was identified following investigation of two unrelated patients of Japanese origin [9]. Both had antibodies to high-prevalence antigens which were non-reactive with K_0 RBCs. Extensive testing with one sample also demonstrated that the antigen is sensitive to dithiothreitol, acid and also to trypsin. The RBCs of both patients had unremarkable Kell phenotypes except that both were KYO+. Sequence analysis of genomic DNA demonstrated homozygosity for c.875G > A in exon 8, which predicts a change of p.Arg292Gln, consistent with the presence of KYO antigen [8]. The antithetical high-prevalence antigen defined by the antibody was named KYOR, and brings the number of antithetical antigen sets in the Kell blood group system to seven.

System 14: Dombrock

DO8 (DOLG) is defined by an antibody to a high-prevalence antigen produced in a patient of Sri Lankan origin. Sequence analysis revealed homozygosity for a new transition, c.674T > A in exon 2 of *DO*A*, which encodes a change of p.Leu225Gln [10]. Serologically, the antibody was compatible with Gy(a−) RBCs, while Hy− RBCs reacted variably. Jo(a−), Do(a+b−) and DOYA− RBCs were incompatible. The patient's RBCs showed weak reactivity with anti-Gy^a but had an otherwise unremarkable Dombrock phenotype. No evidence of haemolytic disease of the foetus and newborn (HDFN) was observed following delivery at 39 weeks of a DAT-negative healthy infant.

System 21: Cromer

Two new high-prevalence antigens have been described in the Cromer blood group system: CROM17 (CRUE) and CROM18 (CRAG). Anti-CRUE was defined following investigation of an antibody in the plasma of a Thai woman with serologic characteristics of a Cromer blood group system antibody. *DAF* sequence analysis revealed heterozygosity for two novel changes in exon 5. In one allele, a transversion c.650T > G encoded the change p.Leu217Trp in the third complement control protein (CCP3) domain of decay accelerating factor (DAF); in the other, a novel nonsense change was observed, of c.639G > A changing p.Trp213Ter,

and thus giving rise to a new null allele of *DAF*. Thus, the absence of the new high-prevalence antigen, CRUE, is most likely due to substitution of p.Leu217Trp.

The CRAG antigen was discovered by the failure of a weakly reactive antibody to an undetermined high-prevalence antigen to react with α-chymotrypsin-treated RBCs, thereby indicating a probable Cromer-related antibody in the plasma of an elderly Greek woman. Known antibodies to high-prevalence Cromer blood group system antigens were ruled out but her plasma was compatible with IFC− RBCs. Exons 2 to 6 were sequenced and a new transition, c.173A > G in exon 2 was identified [11]. This changes p.Asp58Gly in CCP1 of DAF. The patient tolerated three units of incompatible blood with no apparent haemolytic sequelae.

System 30: RHAG

A second low-prevalence antigen has been described in the RHAG blood group system, following the investigation of a case of severe HDFN in an infant who required exchange transfusion [12]. The mother's plasma was negative in a routine antibody screen but reacted strongly with the father's RBCs. The reactivity was characteristic of an Rh antibody but sequencing of the father's *RHD* and *RHCE* genes was unremarkable; however, sequence analysis of *RHAG* revealed homozygosity for two nucleotide changes in exon 6: a missense change c.808G > A, which alters p.Val270Ile; and a silent polymorphism, c.861G > A. Interestingly, homozygosity for both alterations has been described before in an Rh_{null} individual [13]. Whilst 270Ile is predicted to sit in a transmembrane-spanning region, these results suggest that a novel antigen is created by the change. This antigen has been assigned the number RHAG4, and like RHAG2, RHAG4 is associated with weakened expression of Rh blood group system antigens [14].

Of note, RHAG3 (DSLK) remains provisionally assigned pending further genetic evidence.

System 31: FORS

FORS is a new blood group system comprising a single antigen, namely FORS1 (Forssman glycosphingolipid antigen). The presence of FORS1 on human erythrocytes is unusual and was shown to be the result of an enzyme-activating amino acid substitution arising from a missense mutation in the human Forssman synthase gene, *GBGT1* [15, 16]. FORS1 was demonstrated biochemically on the RBCs of two blood donors in different families with the A_{pae} phenotype, first described in 1987 [17]. A_{pae} had been previously thought to constitute a subgroup of A in the ABO system but has now been shown to be based on the presence of FORS1 antigen in the originally described families in which two propositi had *ABO* genotypes homozygous for *O* alleles (with c.261delG), and hence were not capable of making A antigen [16]. DNA sequence analysis of *GBGT1* in these two individuals showed that both were heterozygous for c.887G > A, which changes arginine at position 296 to glutamine. One of the donors was also heterozygous for a nonsense change c.363C > A causing a premature stop codon that was demonstrated to be *in trans* to 887A. Furthermore, the second donor was shown to be homozygous for a third polymorphism, c.58C > T (p.Leu20Phe), demonstrating that 887A exists on two independent allelic backgrounds.

Expression studies performed in the MEG-01 cell line demonstrated that a change of p.Arg296Gln could induce FORS1 expression on the cell surface. A mechanism for the activated synthesis was proposed based on three-dimensional modelling of Forssman synthase, using the crystal structure of the closely related ABO transferase [18]. This indicates that the exchange of arginine by glutamine permitted the enzyme to make contact with the UDP-donor sugar and thus catalyse synthesis of the terminal 3-α-*N*-acetylgalactosamine to its globoside acceptor. FORS1 is not usually found on the RBCs of primates but is highly expressed on the RBCs and uroepithelia of lower mammals such as dogs, sheep and many others. Interestingly, all primates have arginine at position 296 in the enzyme whilst FORS-positive animals have glutamine, consistent with the data discussed above. An independent study also showed the genetic basis of human Forssman negativity and found that Gly230 and Gln296 in the *GBGT1*-encoded enzyme are crucial for enzyme activity, whilst the human consensus is Ser230 and Arg296, supporting the role of p.Arg296Gln as an activating change [19].

System 32: JR

The high-prevalence antigen Jr^a has been promoted to a new blood group system, JR, following the independent findings of two groups that demonstrated the Jr(a−) phenotype was due to inactivating nucleotide changes in *ABCG2* [20, 21]. Zelinski and colleagues used SNP array analysis to pinpoint the *ABCG2* locus on the long arm of chromosome 4 (4q22·1) that demonstrated SNP identity in a pair of Jr(a−) siblings of Caucasian descent and another Jr(a−) sibling pair of Asian descent as well as two unrelated Jr(a−) people. Sequence analysis of *ABCG2* in these six individuals identified different nonsense changes (see Table 3).

Saison and colleagues used a biochemical approach to isolate the Jr^a glycoprotein from cat erythrocytes (which were shown to express Jr^a antigen very strongly) using immunoprecipitation with a monoclonal anti-Jr^a. Identification of a candidate protein by mass spectrophotometric analysis resulted in the investigation of human *ABCG2* and the identity of eight different inactivating changes in 20 individuals. Both groups found two prominent mutations in the two populations in which the Jr(a−) phenotype is found more often (Table 3): in the Romani population, the Jr(a−) phenotype was most often associated with c.706C > T (p.Arg236Ter), while in the Japanese, a transition of c.376C > T (p.Gln126Ter) was the most common change among the Jr(a−) individuals studied. This latter SNP is not uncommon in the Japanese and Korean populations. Subsequently, other mutations have been shown to account for the Jr(a−) phenotype and these are listed in Table 3.

ABCG2 is a multipass membrane protein family member of the ATP-binding cassette transporters and is broadly distributed throughout the body. It has long been associated with drug resistance in cancer and resistance to xenobiotics [22].

System 33: Lan

The Lan antigen has been also elevated to a new blood group system following the work of Helias *et al.* [23]. In studies similar to those described above for Jr^a, the high-prevalence Lan antigen was shown to be carried on ABCB6, another ATP-binding cassette transporter molecule on the erythrocyte membrane. Ten different inactivating changes in *ABCB6* were identified in eleven unrelated Lan− individuals (Table 4) and subsequently, other mutations have been identified in Lan− and Lan^{+w} individuals [24, 25]. Unlike Jr^a, Lan is not associated with any one geographical or ethnic group, which is mirrored by the diversity of mutant alleles in the Lan− individuals studied. ABCB6 is associated with porphyrin transport and was thought to have an important role in heme synthesis [26] however, the existence of ABCB6-deleted individuals indicates that there may be compensation by other transporters in the absence of ABCB6.

Gene terminology

The Working Party continues to update the allele nomenclature tables, and these can be found on the ISBT website (www.isbt-web.org). An expansion of these tables is anticipated and a more detailed monograph on guidelines and usage is planned.

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Table 1

New antigens added to existing blood group systems

Blood group system	Antigen number	Alternative name	Prevalence	Molecular basis Amino acid change	Reference
P1PK	P1PK4	NOR	Low	*A4GALT* c.631C > G p.Gln211Glu	[1]
RH	RH60	PARG	Low	*RHCE* c.501G > A p.Met167Ile	[3]
RH	RH61	CEVF	High	*RHCE* c.667G > T p.Val223Phe	[4]
KEL	KEL36	KETI	High	*KEL* c.1391C > T p.Thr464Ile	[5]
KEL	KEL37	KHUL	High	*KEL* c.877C > T p.Arg293Trp	[7]
KEL	KEL38	KYOR	High	*KEL* c.875G > A p.Arg292Gln	[9]
DO	DO8	DOLG	High	*ART4* c.674T > A p.Leu225Gln	[10]
CROM	CROM17	CRUE	High	*CROM* c.650T > G p.Leu217Trp	[27]
CROM	CROM18	CRAG	High	*CROM* c.173A > G p.Asp58Gly	[11]
RHAG	RHAG4		Low	*RHAG* c.808G > A p.Val270Ile	[12]

Nucleotide and protein changes are written in accordance with *Recommendations for the description of protein sequence variants (v2.0)* from the Human Genome Variation Society (http://www.hgvs.org/mutnomen/recs-prot.html).

Table 2

The 3 new blood group systems and antigens

ISBT System number	System name	System symbol	Antigen name	Antigen symbol	Gene name
031	FORS	FORS	FORS1	FORS1	*GBGT1*
032	JR	JR	Jr^a	JR1	*ABCG2* (*JR*)
033	Lan	LAN	Lan	LAN1	*ABCB6* (*LAN*)

Table 3

Alleles in the JR blood group system

Reference allele *ABCG2*01* encodes JR1 (Jr[a])					
Phenotype	**Allele name**	**Nucleotide change**	**Intron/Exon**	**Amino acid change[a]**	**Reference**
Jr(a+)	*ABCG2*01*				
Null phenotypes					
Jr(a−)	*ABCG2*01N.01*	c.376C > T	Exon 4	p.Gln126Ter	[20, 21]
Jr(a−)	*ABCG2*01N.02·01*	c.706C > T	Exon 7	p.Arg236Ter	[20, 21]
Jr(a−)	*ABCG2*01N.02·02*	c.34G > A	Exon 2	p.Val12Met	[20]
		c.706C > T	Exon 7	p.Arg236Ter	
Jr(a−)	*ABCG2*01N.03*	c.736C > T	Exon 7	p.Arg246Ter	[20]
Jr(a−)	*ABCG2*01N.04*	c.337C > T	Exon 4	p.Arg113Ter	[28]
Jr(a−)	*ABCG2*01N.05*	c.784G > T	Exon 7	p.Gly262Ter	[28]
Jr(a−)	*ABCG2*01N.06*	c.34G > A	Exon 2	p.Val12Met	[28]
		c.1591C > T	Exon 13	p.Gln531Ter	
Jr(a−)	*ABCG2*01N.07*	c.187_197delATATTATCGAA	Exon 2	p.Ile63fs	[21]
Jr(a−)	*ABCG2*01N.08*	c.542_543insA	Exon 6	p.Phe182fs	[21]
Jr(a−)	*ABCG2*01N.09*	c.730C > T	Exon 7	p.Gln244Ter	[21]
Jr(a−)	*ABCG2*01N.10*	c.791_792delTT	Exon 7	p.Leu264fs	[21]
Jr(a−)	*ABCG2*01N.11*	c.875_878dupACTT	Exon 8	p.Phe293fs	[21]
Jr(a−)	*ABCG2*01N.12*	c.1111_1112delAC	Exon 9	p.Thr371fs	[21]
Jr(a−)	*ABCG2*01N.13*	c.34G > A	Exon 2	p.Val12Met	[28]
		c.244_245insC	Exon 3	p.Thr82fs	
Jr(a−)	*ABCG2*01N.14*	c.1017_1019delCTC	Exon 9	p.Ser340del	[29]
Altered phenotypes					
Jr(a+[w])	*ABCG2*01W.01*	c.421C > A	Exon 5	p.Gln141Lys	[29]
Jr(a+[w])	*ABCG2*01W.02*	c.1858G > A	Exon 16	p.Asp620Asn	[29]

[a]For more details regarding the amino acid changes, consult the ISBT Working Party pages at http://www.isbtweb.org/working-parties/red-cell-immuno-genetics-and-blood-group-terminology/blood-group-terminology/.

Table 4

Alleles in the Lan blood group system

Reference allele *ABCB6*01* encodes LAN1 (Lan)					
Phenotype	**Allele name**	**Nucleotide change**	**Intron/Exon**	**Amino acid change[a]**	**Reference**
Lan+	*ABCB6*01*				
Null phenotypes					
Lan−	*ABCB6*01N.01*	c.197_198insG	Exon 1	p.Ala66fs	[23]
Lan−	*ABCB6*01N.02*	c.717G > A	Exon 3	p.Gln239Ter	[23]
Lan−	*ABCB6*01N.03*	c.953_956delGTGG	Exon 4	p.Gly318fs	[23]
Lan−	*ABCB6*01N.04*	c.1533_1543dup CGGCTCCCTGC	Exon 9	p.Leu515fs	[23]
Lan−	*ABCB6*01N.05*	c.1709_1710delAG	Exon 11	p.Glu570fs	[23]
Lan−	*ABCB6*01N.06*	c.1690_1691delAT	Exon 11	p.Met564fs	[23]
Lan−	*ABCB6*01N.07*	c.1867delins AACAGGTGA	Exon 14	p.Gly623fs	[23]
Lan−	*ABCB6*01N.08*	c.1942C > T	Exon 14	p.Arg648	[23]
Lan−	*ABCB6*01N.09*	c.1985_1986delTC	Exon 15	p.Leu662fs	[23]
Lan−	*ABCB6*01N.10*	c.2256 + 2t > g	Intron 16	Splicing defect	[23]
Lan−	*ABCB6*01N.11*	c.1236G > A	Exon 6	p.Trp412Ter	[24]
Lan−	*ABCB6*01N.12*	c.1558_1559insT	Exon 9	p.Val520fs	[24]
Lan−	*ABCB6*01N.13*	c.574C > T	Exon 2	p.Arg192Trp	[24, 25]
Lan−*b*	*ABCB6*01N.14*	c.85_87delTTC	Exon 1	p.Phe29del	[25]
Lan−*b*	*ABCB6*01N.15*	c.376delG	Exon 1	p.Val126fs	[24]
Altered phenotypes					
Lan+w/−	*ABCB6*01W.01*	c.826C > T	Exon 3	p.Arg276Trp	[24, 25]
Lan+w	*ABCB6*01W.02*	c.1028G > A	Exon 5	p.Arg343Gln	[24]
Lan+w	*ABCB6*01W.03*	c.1762G > A	Exon 12	p.Gly588Ser	[24, 25]
Lan+w/−	*ABCB6*01W.04*	c.2216G > A	Exon 16	p.Arg739His	[24]

[a]For more details regarding the amino acid changes, consult the ISBT Working Party pages at http://www.isbtweb.org/working-parties/red-cell-immuno-genetics-and-blood-group-terminology/blood-group-terminology/.

[b]Presumed.