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International society of blood transfusion working party on red cell immunogenetics and terminology: report of the Seoul and London meetings

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Abstract

The Working Party has met twice since the last report: in Seoul, South Korea 2014, and in London, UK 2015, both in association with the International Society of Blood Transfusion (ISBT) Congress. As in previous meetings, matters pertaining to blood group antigen nomenclature were discussed. Eleven new blood group antigens were added to seven blood group systems. This brings the current total of blood group antigens recognized by the ISBT to 346, of which 308 are clustered within 36 blood groups systems. The remaining 38 antigens are currently unassigned to a known blood group system.

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Conflict of interests

The authors declare no conflict of interest.

Keywords

blood groups; genetics; terminology

The Working Party has met twice since the last report: in Seoul, South Korea 2014, and in London, UK 2015, both in association with the International Society of Blood Transfusion (ISBT) Congress. As in previous meetings, matters pertaining to blood group antigen nomenclature were discussed.

A total of seven blood group antigens were added to four of the current blood group systems (Table 1). Three new blood group systems were created, one *de novo* (CD59), and two others Vel (VEL) and Augustine (AUG), elevating the previously homeless high-incidence antigens Vel and At^a, respectively. This brings the current total of recognized blood group antigens to 346, of which 308 are clustered within 36 blood group systems. Thus, there remain 38 serologically defined antigens that have not been assigned to a blood group system as yet. Six of those are in the high prevalence series (901), 17 in the low prevalence series (700) and a further 15 reside in one of six collections (the 200 series).

New blood group antigens

System 2: MNS

Two antigens have been added to the MNS system. Exome sequence analysis of samples from SARA+ and SARA- family members [1] identified a single nucleotide change c.240G>T in exon 3 of *GYPA*, which changes p.Arg80Ser. Sequence analysis of unrelated SARA+ samples confirmed the causative polymorphism [2]. The provisionally assigned number MNS47 was ratified by the working party and the low-prevalence series number 700052 has been made obsolete.

Molecular characterization of the GP.Kip and GP.Yak hybrid glycoporphins showed that they were one and the same and are encoded by the same *GYP(B-A-B)* hybrid that produces Mur, Hil, MUT, MINY, as well as the antigen KIPP [3, 4]. KIPP is recognized by the anti-Hop +Nob sera, Anek and Raddon, but not by antisera specific for the Hop or Nob antigens; as well as by the original anti-Kipp serum [5]. The resulting GP(B-A-B) hybrid retains p.Ser51, which distinguishes this hybrid protein from other known GP(B-A-B) hybrids, which have p.Tyr51. The provisionally assigned number MNS48 was ratified by the working party.

System 5: Lutheran

A new high-prevalence antigen, LUIT was assigned to the Lutheran blood group system based on the serology (LU23) and the identification of two changes in *LU*: sequencing showed two novel homozygous mutations, one in exon 4, c.469G>A (p.Gly157Arg), and one in exon 10, c.1289C>T (p.Thr430Ile). [6]. There was insufficient evidence to determine which of the amino acids are responsible for the absence of the antigen, and thus, the allele number remains provisional: *LU*02.-23*. The proband's RBCs typed Lu: -1,2,3,4,5,6w, 8,13, although the weakening of LU6 expression is not understood.

A second new high-prevalence antigen named LUGA (LU24) was assigned to Lutheran based on the serology and the identification of a single missense change c.212G>A (p.Arg71His) in exon 3 of *LU* [7]. The proband's plasma failed to react with Lu: -12 and Lu: -17 RBCs, as well as Lu(a-b-) RBCs and her own cells. However, anti-Lu12 could be excluded since the RBCs of the proband were reactive with anti-Lu12, and anti-Lu17 could be excluded based on the sequencing results which predicted homozygosity for Lu17. The serology may also be explained in part by the location of the novel amino acid change, which is predicted to lie in the first extracellular immunoglobulin domain of the Lu glycoprotein that also expresses Lu12, LURC, Lu^a/Lu^b, Lu21, Lu5 and Lu17. In addition, homozygosity for two silent changes were observed in exon 6 (c.711C>T and c.714C>T).

System 14: Dombrock

Two new high-prevalence antigens were assigned to the Dombrock blood group system, based both on serology and molecular analysis. The first, named DOLC, was based on the serology (DO9) and the identification of the c.566C>T (p.Thr189Met) change in exon 2 of *DO*. The proposita's RBCs typed Do(a+b-), Hy+, Jo(a+), DOYA+, DOLG+ and her plasma was non-reactive with Gy(a-) RBCs and only weakly reactive with Hy- RBCs [8]. Similarly, an antibody with serological characteristics consistent with Dombrock antibodies, in that it was nonreactive with trypsin-treated RBCs and weakly reactive only with DTT-treated RBCs, was shown to be directed at a new high-prevalence antigen, subsequently named DODE. Molecular analysis identified a c.405C>A (p.Asp135Glu) change in exon 2 of *DO* [9]. The antigen was assigned as DO10.

System 28: GLOB

PX2, a carbohydrate antigen belonging to the GLOB collection (209) and determined by a terminal β 3-*N*-acetyl-galactosamine added to paragloboside, was shown to be the product of *B3GALNT1*, also known as the P antigen synthase [10]. PX2 was therefore reclassified as a member of the GLOB blood group system (028). The P antigen was previously assigned the name GLOB1 (028001), and thus, PX2 was named GLOB2 (028002). This leaves LKE as the sole remaining antigen in the GLOB (209) collection, and the former PX2 number, 209004, was made obsolete.

New blood group systems

System 34: VEL

A founder mutation in the previously undescribed small integral protein 1 (*SMIMI*) gene, c.64_80delGTCAGCCTAGGGGCTGT, was identified as the primary molecular basis underlying the Vel- phenotype [11–13]. The presence or absence of Vel antigen was directly correlated to the presence or absence of SMIM1, a single-pass integral membrane protein. The considerable variation in antigen strength was shown not only to correlate with zygosity for the wild-type *SMIMI* but could also be affected by two rare missense mutations, c.152T>A and c.152T>G (encoding p.Met51Lys and p.Met51Arg, respectively). Furthermore, a single nucleotide polymorphism in intron 2 (rs1175550) situated in a GATA-1 binding site also considerably influenced Vel antigen expression [12, 14, 15].

Based on the molecular and biochemical evidence, Vel was assigned blood group system status (034); system name: Vel; symbol: VEL, antigen: VEL1 (034001). There was no molecular evidence that ABTI was dependent on SMIM1 for expression, despite historical serological evidence of a phenotypic association [16]. As a consequence, collection 200212 was made obsolete and ABTI was returned to the 901 series and reassigned its old number (901015).

As yet, the function of SMIM1 remains unknown; however, elegant work by Arnaud and colleagues has suggested the protein to be a type 2 integral membrane protein [17].

System 35: CD59

Based on the publication of a case report in which a young patient with a CD59 deficiency produced an alloantibody specific for CD59, blood group status was unanimously assigned [18–20]. Both the blood group system and symbol are CD59 (035), and the antigen defined by the antibody maker in this case report has been named CD59.1.

System 36: AUG

The erythrocyte protein, equilibrative nucleoside transporter 1 (ENT1), was identified as the carrier of the At^a antigen. Daniels and colleagues showed that the At(a–) phenotype in individuals of African origin is defined by an amino acid polymorphism on the ENT1 protein (c.1171G>A; p.Glu391Lys) and that the At(a–) members of a family affected by bone malformation lacked the protein due to an inactivating mutation in the *ENT1* gene: c.589+1G>C [21]. Based on the evidence, and following a discussion on names, the blood group system Augustine (symbol AUG) was created (036). The antigen defined by the antibody produced by the null phenotype was named AUG1, and the antigen defined by the amino acid Glu391 (At^a) was named AUG2.

Gene terminology

The Working Party continues to update the allele nomenclature tables and these can be found on the ISBT website. (<http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/>) We anticipate an expansion of these tables, and a more detailed monograph on guidelines and usage is planned.

Acknowledgments

Since the last report [22], Dr Philippe Rouger and Dr Lung-Chi Yu resigned from the Working Party. We sincerely thank them for their helpful contributions during the years. We also note with sadness the passing of our dear colleague Professor George Garratty, who was an active member of the Working Party to the end. As members of the Working Party, all authors have contributed equally to the discussion and conclusions drawn in this paper. CAH is funded by the Australian Red Cross Blood Service and acknowledges the Australian Governments that fund the Blood Service for provision of blood, blood products and services to the Australian Community.

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Table 1

New antigens added to blood group systems

Blood group system	Antigen number	Alt. name	Prevalence	Molecular basis	Protein change
MNS	MNS47	SARA	Low	<i>GYPA</i> c.240G>T	p.Arg80Ser
MNS	MNS48	KIPP	Low	<i>GYP(B-A-B)</i> hybrid	p.Ser51 ^a GPB(1-26)-GPwB(27-54)-GPA(55-57)-Bs(58-103)
LU	LU23	LUIT	High	<i>LU</i> c.469G>A, 1289C>T	p.Gly157Arg, p.Thr430Ile
LU	LU24	LUGA	High	<i>LU</i> c.212G>A	p.Arg71His
DO	DO9	DOLC	High	<i>ART4</i> c.566C>T	p.Thr189Met
DO	DO10	DODE	High	<i>ART4</i> c.405C>A	p.Asp135Glu
GLOB	GLOB2	PX2	High ^b	<i>B3GALNT1</i>	<i>c</i>
Vel	VEL1	Vel	High	<i>SMIMI</i> c.64_80delGTCAGCCCTAGGGGCTGT	p.Ser22Glnfs*270
CD59	CD59.1	-	High	<i>CD59</i> c.146delA	p.Asp49Valfs*31
AUG	AUG1	-	High	<i>ENT1</i> c.589 + 1G>C	p.Ser197fs
AUG	AUG2	At ^a	High	<i>ENT1</i> c.1171G>A	p.Glu391Lys

^aDistinguishes this protein from other known GP(B-A-B) hybrids.^bAlthough PX2 is a product of β 1,3GalNAc-T1 and therefore present on RBCs of common phenotype, it is absent from RBCs of P_1^k and P_2^k phenotypes whilst highly expressed on RBCs of the p phenotype.^cThus, all mutations causing the of P_1^k and P_2^k phenotypes also cause lack of PX2.

Table 2

New blood group systems

Blood group system	Symbol	Number	Reference sequence	Number of antigens	References
Vel	VEL	034	NM_001163724	1	Storry, Jönd <i>et al.</i> [11], Cvejic <i>et al.</i> [12], Ballif <i>et al.</i> [13]
CD59	CD59	035	NM_000611.5	1	Anliker <i>et al.</i> [19], Hochsmann <i>et al.</i> [20]
Augustine	AUG	036	NM_001078175.2	2	Daniels <i>et al.</i> [21]