HHS Public Access

Author manuscript

Vox Sang. Author manuscript; available in PMC 2023 November 27.

Published in final edited form as:

Vox Sang. 2022 November ; 117(11): 1332–1344. doi:10.1111/vox.13361.

International Society of Blood Transfusion Working Party on Red Cell Immunogenetics and Blood Group Terminology Report of Basel and three virtual business meetings: Update on blood group systems

Christoph Gassner[1], **Lilian Castilho**[2], **Qing Chen**[3], **Frederik Banch Clausen**[4], **Gregory A. Denomme**[5], **Willy A. Flegel**[6], **Nick Gleadall**[7], **Åsa Hellberg**[8], **Yanli Ji**[9], **Margaret A. Keller**[10], **William J. Lane**[11], **Peter Ligthart**[12], **Christine Lomas-Francis**[13], **Nuria Nogues**[14], **Martin L. Olsson**[8,15], **Thierry Peyrard**[16,17], **Jill R. Storry**[8,15], **Yoshihiko Tani**[18], **Nicole Thornton**[19], **Ellen van der Schoot**[20], **Barbera Veldhuisen**[12,20], **Franz Wagner**[21,22], **Christof Weinstock**[23], **Silvano Wendel**[24], **Connie Westhoff**[13], **Vered Yahalom**[25], **Catherine A. Hyland**[26]

[1]Institute of Translational Medicine, Private University in the Principality of Liechtenstein, Triesen, Liechtenstein

[2]University of Campinas/Hemocentro, Campinas, Brazil

[3]Jiangsu Province Blood Center, Nanjing, Jiangsu, China

[4]Department of Clinical Immunology, Laboratory of Blood Genetics, Copenhagen University Hospital, Copenhagen, Denmark

[5]Grifols Laboratory Solutions, San Marcos, Texas, USA

[6]Department of Transfusion Medicine, NIH Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

[7]Department of Haematology, University of Cambridge and NHS Blood and Transplant, Cambridge Biomedical Campus, Cambridge, UK

[8]Department of Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, Sweden

[9]Institute of Clinical Blood Transfusion, Guangzhou Blood Center, Guangzhou, People's Republic of China

Correspondence Christoph Gassner, Institute of Translational Medicine, Private University in the Principality of Liechtenstein, Dorfstrasse 24, 9495 Triesen, Liechtenstein. christoph.gassner@ufl.li.

CONFLICT OF INTEREST

C.G. acts as a consultant to inno-train Diagnostik GmbH, Kronberg i. T., Germany. Procedures for the molecular detection of *GYPB* deletions for S-s-U- phenotype diagnostics have been granted as a European patent (EP 3 545 102 B1). A similar content patent US application is pending. G.A.D. is a transfusion education consultant for Abbott Laboratories, Chicago, IL. W.J.L. is a member of the Scientific Advisory Board of CareDx, Inc. and his institution is a founding member of the Blood Transfusion Genomics Consortium (BGC) that has received fees from Thermo Fisher Scientific Inc. to help co-develop a high-density DNA genotyping array. C.M.W. is a member of the Scientific Advisory Board of Quotient. N.G., M.L.O. and J.R.S. have no conflicts of interest with regard to this manuscript. L.C., Q.C., F.B.C., W.A.F., A.H., J.Y., M.A.K., P.L., C.L.F., N.N., T.P., Y.T., N.T., E.V.D.S., B.V., F.F.W., C.W., S.W., V.Y. and C.H. have no conflicts of interest.

The views expressed do not necessarily represent the view of the National Institutes of Health, the Department of Health and Human Services, or the US Federal Government.

[10]American Red Cross Blood Services, Philadelphia, Pennsylvania, USA

[11]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[12]Department of Diagnostic Immunohematology, Sanquin, Amsterdam, The Netherlands

[13]Laboratory of Immunohematology and Genomics, New York Blood Center Enterprise, New York, New York, USA

[14]Banc de Sang i Teixits, Barcelona, Spain

[15]Department of Laboratory Medicine, Division of Hematology and Transfusion Medicine, Lund University, Lund, Sweden

[16]Etablissement Français du Sang Ile-de-France, Centre National de Référence pour les Groupes sanguins, Ivry-sur-Seine, France

[17]UMR_S1134 Inserm Université Paris Cité, Paris, France

[18]Osaka Red Cross Blood Center, Osaka, Japan

[19]International Blood Group Reference Laboratory, NHS Blood and Transplant, Bristol, UK

[20]Department of Experimental Immunohematology, Sanquin, Amsterdam, The Netherlands

[21]German Red Cross Blood Service NSTOB, Springe, Germany

[22]MVZ Clementinenkrankenhaus, Springe, Germany

[23]Department of Transfusion Medicine, Institute for Clinical Transfusion Medicine and Immunogenetics, German Red Cross Blood Service, Ulm, Germany

[24]Blood Bank, Hospital Sirio-Libanes, São Paulo, Brazil

[25]Rabin Medical Center, Petach Tiqva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[26]Australian Red Cross Lifeblood, Brisbane, Australia

Abstract

Background and Objectives: Under the ISBT, the Working Party (WP) for Red Cell Immunogenetics and Blood Group Terminology is charged with ratifying blood group systems, antigens and alleles. This report presents the outcomes from four WP business meetings, one located in Basel in 2019 and three held as virtual meetings during the COVID-19 pandemic in 2020 and 2021.

Materials and Methods: As in previous meetings, matters pertaining to blood group antigen nomenclature were discussed. New blood group systems and antigens were approved and named according to the serologic, genetic, biochemical and cell biological evidence presented.

Results: Seven new blood group systems, KANNO (defined numerically as ISBT 037), SID (038), CTL2 (039), PEL (040), MAM (041), EMM (042) and ABCC1 (043) were ratified. Two (039 and 043) were de novo discoveries, and the remainder comprised reported antigens where the causal genes were previously unknown. A further 15 blood group antigens were added to the

existing blood group systems: MNS (002), RH (004), LU (005), DI (010), SC (013), GE (020), KN (022), JMH (026) and RHAG (030).

Conclusion: The ISBT now recognizes 378 antigens, of which 345 are clustered within 43 blood group systems while 33 still have an unknown genetic basis. The ongoing discovery of new blood group systems and antigens underscores the diverse and complex biology of the red cell membrane. The WP continues to update the blood group antigen tables and the allele nomenclature tables. These can be found on the ISBT website (http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/).

Keywords

blood groups; genetics; genomics; red cell antigens; terminology

INTRODUCTION

The International Society of Blood Transfusion (ISBT) Working Party (WP) for Red Cell Immunogenetics and Blood Group Terminology is responsible for the ratification and naming of blood group systems and antigens. Since the last report, which included developments up to the Toronto meeting in 2018 [1], the WP has held four business meetings. One took place physically in Basel, Switzerland, in conjunction with the 2019 ISBT Regional Congress, and three were held as virtual meetings during the COVID-19 pandemic in 2020 and 2021.

Requests for new blood group systems and antigens were presented at these meetings and accepted according to previously established criteria [2]. Criteria for defining a blood group system include evidence that it is a discrete genetic entity under the control of a single gene or by contiguous homologous genes, in which different antigens within a system are encoded by alternative forms of the gene. All blood group antigens must be defined serologically by a specific antibody formed by a human lacking the antigen in question and shown to be inherited.

Some red cell antigens do not belong to a blood group system because their molecular bases have not been defined. The ISBT WP classifies these antigens into collections or series. There are two series of antigens designated the 700 and 901 series, which represent, respectively, antigens with a prevalence within the population of study of less than 1% or greater than 90%.

This report summarizes the evidence presented in ratifying seven new blood group systems and 15 new antigens over the four meetings. These included antigen(s) previously in the 700 or 901 series, which were transferred into existing or into new blood group systems [2].

NEW BLOOD GROUP SYSTEMS

Seven new blood group systems (designated ISBT 037–043) were registered over the four meetings (Table 1). Only two, CTL2 and ABCC1, comprised de novo antigens, while the other five resolved the genes responsible for expression of previously reported high-prevalence antigens, four formally classified in the 901 series.

System 037: KANNO—An antibody to a high-prevalence antigen, designated KANNO (now KANNO1), was first identified in 1991 in a Japanese woman with a history of pregnancy, although never formally listed in the 901 series [3]. Definitive evidence presented at the Basel meeting showed that KANNO was encoded by the *PRNP* gene at chromosome 20p13. Genome-wide association studies defined single nucleotide variants (SNVs) in four unrelated individuals, with anti-KANNO, which were absent in 415 healthy Japanese. Whole-exome sequencing using 14 unrelated KANNO antigen-negative (KANNO−) individuals then implicated the causal variant, rs1800014 c.655G>A on *PRNP*, resulting in p.Glu219Lys. Family studies supported the genotype and phenotype associations. Monoclonal antibody-specific immobilization of erythrocyte antigen assays showed the KANNO antigen is on the prion protein, as did transfection and expression studies. The *PRNP*655A* variant in the ExAC database has a frequency of 5.8% in Japan, 4% in South and East Asia, 0.03% in Africa and 0.004% in Europe [4].

There is only one antigen in the KANNO system, which is defined as KANNO1 or, under the numerical designation, ISBT 037001 (Table 1). KANNO is named after the first proposita [3].

System 038: SID

The Sd^a antigen was first described in 1967 and classified in the ISBT 901 series as ISBT 901012. The chemical basis of the antigen was known to be a terminal trisaccharide, (GalNAcβ1–4 (NeuAcα2–3)Galβ-R) and a candidate histo-blood group gene, the *B4GALNT2*, chromosomal location 17q21.32, had been cloned in 2003. Nevertheless, the genetic basis for the Sd(a−) phenotype remained unknown. While approximately 10% of Caucasians have Sd(a−) red blood cells (RBCs), only 2%–4% are truly negative and can make anti-Sd^a. The reason is that the Sd^a antigen is also present in other tissues. Against this known background, the evidence presented in Basel, from Sanger sequencing and allele discrimination assays, defined genetic variants in *B4GALNT2* that associate with the Sd(a−) phenotype. The most common variant observed was a variant (rs7224888:C) in exon 10 with an allele frequency of approximately 0.10. This c.1396T>C variant causes a p.Cys466Arg change, and six of nine Sd(a−) individuals were homozygous for c.1396C. One individual was compound heterozygous for rs7224888/rs72835417, the latter being a splice-site variant in intron 8. Another individual was also a compound heterozygote but for low-frequency variants rs148441237 and rs61743617. Finally, one sample had no detectable deviations from the consensus sequence, a finding that warrants further investigation [5]. In addition, an abstract describing another nine Sd(a−) individuals reported eight to be homozygous for c.1396C (rs7224888:C) and one compound heterozygous for rs7224888/rs72835417 [6].

Expression and glycoproteomic studies with *B4GALNT2* constructs with wild-type sequence or the predominant null candidate variant c.1396C were performed in HEK293 cells [7]. While the consensus ‘wild-type’ allele induced expression of the antigen, the c.1396C construct did not. This variant also resides in a haplotype block associated with a long non-coding (lnc) RNA, and downregulation of this lnc RNA correlates with poor prognosis in cancer, which may be marked by loss of Sd^a. The Sd^a antigen is also involved

in the pathogenesis of different infections, and high expression of Sd^a has been correlated to protection against parasite invasion of RBCs [8–10].

The Sd^a antigen was moved from the 901 series (901012) into a new blood group system, SID, ISBT 038 and is the only known antigen in this system (Table 1). SID is one of the eight carbohydrate histo-blood group systems with wide tissue distribution and which depend on genetic variants altering glycosyltransferase activity and/or specificity. The name SID was originally in honour of the head of the maintenance department of the Lister Institute that housed the Race and Sanger laboratory in London, who was the source of the first so-called super-Sid or Sd(a++) control cells [11].

System 039: CTL2

Studies leading to assigning the CTL2 blood group system were initiated by a sample from a pregnant woman who presented with an antibody reacting against a high-prevalence antigen on RBCs. Compatibility testing showed five unrelated patients from Morocco and one female patient from Europe lacking this high-prevalence antigen. Whole-exome sequencing on the Moroccan samples identified the *SLC44A2* gene (also known as *CTL2*) on chromosome 19p13.2 as a primary candidate. Genomic DNA sequencing identified SNV c.1192C>A in all Moroccan samples, associated with amino acid change (p.Pro398Thr) on the third extracellular loop of the protein. L-929 cells transfected with the *SLC44A2* variant carrying c.1192A were non-reactive with the antibody, confirming the loss of this antigen associated with this amino acid change [12]. Conversely, overexpression of *SLC44A2* in L-929 cells demonstrated the antigen (Peyrard, personal communication, June 22, 2019).

The European patient exhibited a large deletion of the *SLC44A2* gene, including exons 1–14, resulting in a null phenotype. This was consistent with the serological data, which showed that while the sera of the Moroccan probands were compatible with RBCs from the European patient, the Moroccan RBCs were incompatible with the antibody from the European patient, indicating that the latter was an antibody directed against the *SLC44A2* protein [12].

There were additional clinically interesting features associated with this gene. *SLC44A2* knockout mice have hearing loss; the proband with null phenotype also has hearing loss in the upper-frequency range. The protein encoded by the *SLC44A2* gene also carries HNA-3 (Human Neutrophil Antigen), which is involved in transfusion-related acute lung injury; the possible association between the HNA-3a/3b status and red cell antigen expression remains unknown. To avoid confusion, the terminology used for the granulocyte antigen system HNA-3 and the blood group system CTL2, both encoded by *SLC44A2*, have not been synchronized but are being kept separate.

Thus, there are two RBC antigens within the CTL2 system (Table 1): one antigen, defined by the antibody in the European proband, is called VER (ISBT 039001) after Verona from the proband's birthplace. The other antigen is called RIF (ISBT 039002) after the geographical region in Morocco from which the patients who lack this antigen originate.

System 40: PEL

The PEL antigen was identified in 1980 and subsequently classified in the 901 series as 901014. PEL− RBCs have been found only in four unrelated French-Canadian families from the province of Quebec. Integrated genomic and proteomic studies were presented to explain this phenotype. Initially, whole-exome sequencing did not reveal any candidate sequence variants among family members. However, a comparative global proteomic analysis of the RBCs pinpointed ABCC4 as the likely candidate protein for PEL antigen expression. Review of exome sequencing data showed a structural change comprising a large deletion of the *ABCC4* gene in all PEL− cases. Sanger sequencing confirmed the same breakpoint. Subsequent western blot and transfection studies confirmed that the PEL blood group antigen is carried on the ABCC4 protein and that homozygosity for a large deletion in the *ABCC4* gene, chromosomal location 13q32.1, is responsible for the rare PEL− phenotype. The carrier protein, ABCC4, is a member of the superfamily of ATP-binding cassette transporters. The JR and LAN blood group systems (ISBT 032 and 033) are carried on by other members of this superfamily. ABCC4 protein is also called MRP4 for Multidrug Resistance Protein 4. The PEL− phenotype is associated with moderately impaired platelet aggregation [13].

PEL is now a new blood group system, ISBT 040, and the antigen transferred from the 901 series, where 901014 becomes obsolete. There is only one antigen known in this system: PEL or ISBT 040001 (Table 1). The name PEL is derived from the name of the first antigen-negative proband who made anti-PEL [14].

System 041: MAM

The MAM-negative phenotype was first described in 1993 in a pregnant woman (MAM.) who presented with an antibody to a high-prevalence antigen. Since then, severe or even fatal haemolytic disease of the fetus and newborn (HDFN) has been reported in such cases. The genetic basis for the MAM antigen remained unresolved, and the antigen was placed in the 901 series as 901016. Studies on samples gathered from 10 MAM-negative individuals were reported at the first virtual meeting. Genomic DNA from five MAM− subjects was subjected to whole-exome sequencing (analysis and a subsequent filtering strategy showed the only candidate gene was *EMP3* [encoding Epithelial Membrane Protein 3]); Sanger sequencing of *EMP3* confirmed variants were present in this gene for all 10 MAM− samples studied. A total of four different allelic variants were defined among the 10 MAM− samples: namely, a total gene deletion, two different single-exon deletions and a substitution that creates a stop codon. The latter is the most commonly encountered and was found in four of the 10 MAM− individuals. Its frequency in the genome aggregation database (gnomAD) is 0.017% (present in 43 of 251,000 alleles) [15].

Subsequent short hairpin (sh)RNA knockdown, CRISPR knock-out and transfection over-expression studies were used to show a causal relationship between *EMP3* and the presence or absence of the MAM antigen. The probands have no apparent clinical phenotype. *EMP3* has been reported to act both as an oncogene and a tumour suppressor gene in different cancers. The presented study showed a marked increase in reticulocyte production from MAM− erythroid cultures suggesting that *EMP3* acts as a suppressor of proliferation in

normal erythropoiesis. It may also have a function in regulating the level and stabilization of CD44 at the cell surface of erythroid progenitors. As a consequence of this, it was shown that MAM− RBCs have consistently low expression of CD44, which affects red cell levels of the antigens in the IN system (ISBT 023) [15].

The MAM antigen was transferred from the 901 series into the MAM blood group system, ISBT 041, where 901016 became obsolete. There is only one known antigen in this system: MAM or ISBT 041001 (Table 1).

System 042: EMM

The new blood group system EMM was reported independently by two teams at the second virtual meeting [16, 17].

Antibodies to a high-prevalence antigen, Emm, were first described in 1987 [18]. One team investigated samples from a 65-year-old Indian male who had presented with anti-Emm, as well as samples from family members. Whole-genome sequencing and variant filtering defined a homozygous 2 bp deletion, c.2624_2625delTA, in the *PIGG* gene for the proband [17]. The heterozygous 2 bp deletion was also observed in two other family members. *PIGG* encodes a glycosylphosphatidyliniositol (GPI) ethanolamine phosphate transferase-2 enzyme. This enzyme is involved in the addition of a side chain modification on the second mannose of a GPI protein anchor in the red cell membrane. Further studies on a frozen sample collection of historic anti-Emm probands from Japan, United States and North Africa, revealed three further loss-of-function mutations in the *PIGG* gene: deletion of exons 2–3, deletion of exons 7–9, insertion–deletion in exon 3 [17]. There are reports of neurological phenotypes, including seizures and developmental delay involving *PIGG* loss of function mutations [19].

An independent team studied samples from three unrelated Emm− individuals, all with anti-Emm. Samples were obtained from cryopreserved reference material. Whole-exome sequencing and data analysis defined three different predicted loss-of-function mutations in the *PIGG* gene three different predicted loss-of-function mutations in the *PIGG* gene: c.640C>T (p.His214Tyr), c.901+1delG, deletion of exon 6. Flow cytometry studies revealed a strong decrease in Emm expression in *PIGG* knockout cells but normal expression of CD59. The CD59 blood group antigen is expressed on the protein portion of the GPI-linked protein. K562 cells deficient of *PIGA* lacked both Emm and CD59, as the GPI was completely absent [16].

In summary, two different approaches demonstrated that the *PIGG* gene, located on chromosome 13, encodes the Emm antigen in this new system, EMM ISBT 042 (Table 1) [16, 17]. The Emm antigen was transferred from the 901 series, making 901008 now obsolete and is defined as ISBT 042001, the only antigen in this system. The name comes from the first antigen-negative proband to make anti-Emm.

System 043: ABCC1

An antibody to an unknown high-prevalence red cell antigen was detected in a young Brazilian man who had been transfused when undergoing a kidney transplant [20]. Parents

of the proband with the antibody were first-degree cousins. Samples were available for study from the proband and three siblings, one of them being compatible with the proband. Whole-exome sequencing, with variant filtering strategy, defined a homozygous large deletion encompassing five exons in the *ABCC1* gene in the proband and the compatible sibling. The other family members were heterozygous. Sanger sequencing was used to define the breakpoints of the deletion. Expression studies in K562 transfected cells showed the antibody to react with the *ABCC1* gene product expressed on the transfected cells. Allele-specific PCR confirmed that the parents were each heterozygous for the deletion.

ABCC1 is reported to play a role in the protection of kidney epithelial cells. Regrettably, the proband died from renal failure further to kidney graft rejection. The proband's brother showed evidence of abundant oxalate crystals in urine, which is a potential early marker for renal disease. The carrier protein ABCC1, a member of the superfamily of ATP-binding cassette transporters, has practical clinical relevance in pharmacogenomics and pharmacokinetics [21]. Other ABC transporters are also known to carry antigens of blood group systems, namely *ABCG2* of the JR system (ISBT 032), *ABCB6* of the LAN system (ISBT 033) and the above *ABCC4* of the PEL system (ISBT 040) [1, 13, 22–24]. ABCC1 was proposed as the carrier of a new blood group system designated ISBT 043, encoded by *ABCC1*. This is the first blood group system encoded by a gene on chromosome 16 (Table 1).

The wild-type allele *ABCC1*01* encodes the high-prevalence WLF antigen after the proband's name, assigned as ISBT 043001. Homozygosity for the null allele, *ABCC1*01N.01*, with the exon deletion, defines the WLF− phenotype.

NEW BLOOD GROUP ANTIGENS IN EXISTING BLOOD GROUP SYSTEMS

Fifteen blood group antigens were added to existing blood group systems over these meetings. These included high- and low-prevalence antigens (Table 2). Of note, one, the Kg antigen, was previously in the 700 series and shown to be on the Rh-associated glycoprotein system (RHAG ISBT 030). The remainder represented de novo discoveries.

System 002: MNS, SUMI (ISBT 002050)

A positive cross-match in a Japanese patient revealed an antibody to an unknown low-prevalence antigen, tentatively named SUMI [25]. Monoclonal anti-SUMI-producing cells (HIRO-305) were established using lymphocytes from a donor having anti-SUMI. SUMI+ RBCs were examined by immunocomplex capture fluorescence analysis, identifying glycophorin A as a carrier candidate of the antigen. Genomic DNA was extracted from whole blood, and the *GYPA* gene of donors with SUMI+ RBCs was shown to carry a c.91A>C (p.Thr31Pro) substitution. The serologic screening revealed that 23 of 541,522 Japanese individuals (0.0042%) were SUMI+, whereas 1351 of 10,392 investigated individuals (13.0%) had alloanti-SUMI. SUMI antigen is sensitive to ficin, trypsin, pronase and neuraminidase, slightly weakened by α-chymotrypsin and resistant to sulfhydryl-reducing agents. Based on their prevalence and chemical sensitivity, anti-SUMI has been suggested to be a naturally occurring IgM. There are now 50 antigens in the MNS system, including SUMI, defined numerically as ISBT 002050.

System 004: Rh, CETW (ISBT 002063)

A genomic study on indigenous Australian individuals revealed two individuals (2/247) heterozygous for an *RHCE* variation c.486C>G. This novel SNV, c.486C>G on the *RHCE* allele predicts an amino acid change, p.Asn162Lys in the third extracellular domain of the RhCE blood group protein. These findings triggered the review of an unre-solved HDFN case involving a woman with an unidentified antibody directed to a low- prevalence antigen present on the paternal and newborn's RBCs. Sequencing showed both the father and the newborn to be heterozygous for the same c.486C>G SNV in *RHCE*.

Extensive serologic testing on the stored maternal plasma and the antibody eluted from the newborn's RBCs showed the maternal antibody reacted with the RBCs from the two indigenous Australians but not with control cells. The combined studies indicate that the c.486C>G SNV generated a novel low-prevalence antigen. The antigen name is 'CETW' with 'TW' representative of the town for the Indigenous Australian study. While there are now 56 antigens defined in the RH system, the ISBT designation of CETW is ISBT 004063, noting that seven antigens have been made obsolete.

System 005: Lutheran LUNU (ISBT 005028) and LURA (ISBT 005029)

Two high-prevalence antigens were added to the Lutheran, LU, blood group system (Table 2). An antenatal patient of Caucasian descent exhibited an unidentified antibody that was reactive with all tested RBCs except examples of In(Lu) cells. Soluble recombinant Lu protein inhibited the antibody. Other known LU high-prevalence antigens were ruled out. Sanger sequencing of all 15 exons of the *BCAM* coding region, which encodes the Lu glycoprotein, identified homozygosity for an SNV, c.121G>A (p.Val41Met). This c.121G>A is listed in the gnomAD database with a frequency of 3.98×10^{-6}. Family studies demonstrated inheritance with the parents and two siblings heterozygous for this allele [26]. This antigen is named LUNU (LU 028), LU for Lutheran and NU from the name of the patient.

The second novel antigen was detected from studies involving an individual of Arab descent with beta-thalassemia intermedia and alpha globin deletion who showed an antibody to a high-prevalence antigen in the LU system. Soluble recombinant Lu protein inhibited the antibody. Sequencing the *BCAM* coding region identified c.1351A>C (p.Lys451Gln) as the only variant in the gene [27]. This antigen is named LURA (LU 029), LU for Lutheran and RA from the name of the patient.

System 010: Diego, DIST (ISBT 010023)

A novel low-prevalence Diego antigen named DIST was characterized by a c.1447G>A SNV in *SLC4A1*, leading to a p.Gly483Ser amino acid change in the extracellular part of the Band 3 protein [28]. This variant was on the *DI*B* allele (phenotype was Di(a−b+)). According to the gnomAD database, this variant is found in one of 113,680 European individuals. The clinical significance of the antibody is unknown. The name of the antigen 'DIST' results from DI for Diego and the first letters of the first names of the person producing the antibody and the antigen carrier, respectively.

The new DIST (DI 010 023) antigen is defined by c.1447G>A (p.Gly483Ser), with a total of 23 antigens now defined in this system.

System 013: Scianna, SCAR (ISBT 013008) and SCAC (ISBT 013009)

Two new antigens, designated SCAR and SCAC, were added to the Scianna, SC system.

The SCAR antigen was identified following the detection of an antibody to a high-prevalence antigen in a patient from Saudi Arabia with sickle cell beta thalassemia [29]. For investigating the antibody specificity, soluble recombinant ERMAP protein was used, which inhibited the antibody in the column agglutination technique. The patient showed no signs of haemolysis following an incompatible blood transfusion. A monocyte monolayer assay (MMA) was negative, indicating a possible low level of clinical significance for this antibody [29].

The genomic sequence of *ERMAP* showed the patient exhibited homozygosity for an *ERMAP* c.424C>G (p.Gln142Glu) variant, for which his two sisters were heterozygous. The c.424C>G variant occurred in the *SC*01* allele. The frequency of the variant was not known since this variant was not reported on any database. The name ‘SCAR’ for the new antigen was derived from SC for the blood group system and AR from the patient’s name. Individuals homozygous for this c.424G allele do not express the high-prevalence SCAR antigen and can produce anti-SCAR. The allele, *SC*01.-08*, occurs in one haplotype with the *RHCE*03* (*RHCE*cE*) allele. The new SCAR (SC 013008) antigen is the eighth antigen of the SC blood group system and the first new SC antigen reported since 2005 [30].

Another new SC antigen, SCAC, was discovered following the identification of an antibody to a high-prevalence antigen in the plasma of a 41-year-old African American female with sickle cell disease (SCD) undergoing kidney biopsy [31]. A compatible sister was found. An MMA was performed and suggested the clinical significance of the antibody. The antibody reacted with ficin, papain, trypsin, α-chymotrypsin and 0.2 M DTT-treated cells. The only non-reactive cells were SC_{null} cells, indicating a probable Scianna-related antibody.

Sequencing of *ERMAP* coding exons found the sample was homozygous for exon 4 changes, c.217C>T (p.Arg73Cys) and c.219C>T (silent), with frequencies of 0.00811 and 0.0838, respectively, in Africans. The c.217T (p.Cys73) change in *ERMAP* suggested the patient had an altered protein, encoded by *SC*01.-09*, identifying a new SC antigen, ISBT 013009, named ‘SCAC’ after SC for Scianna and AC for the amino acid changes (Arg to Cys).

Analogous to the SCAR antigen, here homozygosity for the *SC*01.-09* allele abolishes expression of SCAC on the ERMAP protein. SCAC is the ninth antigen in the SC system (Table 2).

System 020: Gerbich, GECT (ISBT 020013) and GEAR (ISBT 020014)

Two new Gerbich, GE, high-prevalence antigens, GECT and GEAR, bring the total number of antigens in this system to 13, noting that one was previously made obsolete.

A sample came from a 13-year-old girl with SCD, recently transfused, who experienced a delayed haemolytic transfusion reaction [32]. The antibody reacted with all panel cells except those with the phenotype GE:−2,3,4 and GE: −2, −3,4. *GYPC* Sanger sequencing revealed homozygosity for a novel SNV, c.59C>T (predicting p.Pro20Leu). The patient's brother, also with SCD, had the same *GE* genotype, but RBCs were not available to test for compatibility. It was concluded that homozygosity of the novel *GYPC*, c.59T (p.Leu20) resulted in the loss of glycophorin C (GPC) epitopes, for example, negativity for the antigen 'GECT'. The *GYPC* c.59C>T has a frequency of 0.01246 in Africans. The proposed antigen name is GECT with GE for Gerbich and CT after the C to T nucleotide exchange. The allele was named *GE*01.−13*.

In a second case, a sample was received from a 38-year-old Caucasian woman with a possible delayed transfusion reaction, whose plasma contained an antibody to a high-prevalence antigen [33]. Phenotypically similar RBCs treated with 0.2 M DTT or α-chymotrypsin were reactive, but the plasma was non-reactive with papain or trypsin-treated RBCs, suggesting possible Gerbich specificity. An eluate containing the antibody was made by adsorption/elution and reactivity patterns suggested anti-Ge3 specificity. However, the patient's RBCs typed Ge2+ and Ge3+ using single donor source antibodies and Ge4+ with monoclonal anti-Ge4. *GYPC* exon sequencing identified a novel homozygous nucleotide change in exon 3, c.118G>A (p.Gly40Arg). This change is present in the dbSNP database with a rare minor allele frequency (MAF) of 0.0000247. A synonymous change c.333A>C in exon 4 was also found. Data were consistent with a novel high-prevalence antigen in the Gerbich system that was named 'GEAR'. Lack of the antigen is predicted to be associated with the homozygous presence of c.118G>A SNV in *GYPC* exon 3 encoding amino acid change p.Gly40Arg in GPC (or p.Gly19Arg in GPD). The role of anti-GEAR as causative in the patient's delayed transfusion reaction is unknown due to the presence of other antibodies. The allele name of the GYPC exon 3 c.118G>A SNV is *GE*01.-14.*

GECT (GE 020013) and GEAR (GE 020014), both of high prevalence, were added to the GE blood group system.

System 022: Knops, KDAS, DACY and YCAD (ISBT 022010, 022011 and 022012)

Three new antigens complete two new antithetic relationships of the Knops (KN) blood group system, KCAM/KDAS and DACY/YCAD, respectively [1, 34–36].

One new antithetic relationship was defined by investigating a Caucasian male patient who had been transfused and who presented with an antibody to a low-prevalence antigen. The antibody reacted with the RBCs of a donor included on an antibody identification panel that lacked the high-prevalence Knops antigen, KCAM. An antigen antithetical to KCAM has not previously been defined. The *CR1* gene encodes the glycoprotein that carries the Knops antigens, and loss of the KCAM antigen is known to arise from CR1 c.4843A>G change, which results in p.Ile1615Val. Additional testing showed this patient's antibody to be non-reactive with KCAM+ cells from 23 individuals homozygous *CR1* c.4843A but reactive with KCAM+ cells from individuals heterozygous *CR1 c.4843A/G* and with KCAM− cells from individuals homozygous *CR1* c.4843G [35].

KCAM is defined by p.Ile1615, and the antithetical antigen to KCAM was named KDAS and is defined by the amino acid change from isoleucine (KCAM) to valine (KDAS). The antigen name KDAS (ISBT 022010) was derived from the name of the proband. The allele for KDAS will be defined as *KN*01.10.*

The second new antithetic relationship within the Knops blood group system is represented by two new KN antigens with unusual, previously unreported locations on the CR1 protein. To date, all previously described antigens of the KN blood group system are located in the long homologous repeat D (LHR-D) of complement receptor 1 (CR1). While there have been reports that some sera react only with the LHR C (LHR-C), the antigens in LHR-C were unknown. Soluble recombinant LHR-C and LHR-D were used to identify antibodies directed to LHR-C of CR1, into which a point mutation was introduced to characterize the underlying blood group antigens [36]. In addition, database studies to define haplotypes of *CR1* were performed. Several antisera were identified that were specific, either against CR1 p.His1208 or against CR1 p.Arg1208, a polymorphism described by rs2274567 and located in LHR-C. It was shown that due to linkage disequilibrium, anti-CR1 p.His1208 might be mistaken for anti-KCAM. In summary, a novel antithetical KN blood group antigen pair was found at position p.1208 of CR1. Antibodies against these two novel antigens seem to contribute to more than a quarter of all KN antibodies in Europe. The names DACY (dual antigen-site of CR1 beyond LHR-D) for CR1 p.His1208 and the reverse name YCAD for CR1 p.Arg1208 were proposed. With these additions, there are now 12 antigens in the KN system.

All four permutations, that is, KCAM encoded together with DACY or YCAD on the same allele, and KDAS encoded together with DACY or YCAD on the same allele, were observed [36]. This permuted polymorphism is found with varying prevalence among the different ethnic groups studied. Moreover, most of these permutations are linked to already recognized *KN* alleles, splitting these latter into up to four different allelic subtypes.

System 026: JMH, JMHN (ISBT 026007) and JMHA (ISBT 026008)

A further antigen was added to the JMH system at the Basel meeting. An antibody to a high-prevalence antigen was identified in a Moroccan individual and shown to be inhibited by soluble recombinant JMH (Table 2). Genomic sequencing revealed homozygosity in the SEMA7A gene for three SNVs. A rare non-synonymous variant, c.709G>A (p.Asp237Asn); a common synonymous change, c.1545A>G (p.Gln515Gln) and a rare non-synonymous c.1865G>A (p.Arg622His). Notably, all antigens in JMH are changes from arginine. Modelling shows that p.Arg622 is exposed out of the RBC membrane, and this may be a critical amino acid [37]. It is noted that this variant has a MAF of 0.002 in Europeans and 0.0008 in Africans in the database that was established by the 1000 Genomes Project Consortium (1KGP), a construct of genome sequences for 2504 individuals [38]. This is the seventh antigen of the JMH blood group system (ISBT 026007), and the proposed allele name is *JMH*01.-07*. The new antigen was designated JMHN, where N stands for North Africa, where all cases of the rare JMH: -7 type have been found to date.

Another novel JMH antigen, JMHA, was described following the serological investigation of plasma from a female Palestinian patient that showed the presence of an antibody to a

high-prevalence antigen [39]. Soluble recombinant JMH blood group proteins were used in inhibition tests. The clinical significance of the antibody was assessed by an MMA and showed a monocyte index <3%, suggesting that the antibody is of minor or negligible clinical relevance. The plasma of the patient was crossmatched with JMH:3, JMH: −5 and JMH: −7 cells, all found to be incompatible, whereas JMH: −1 cells were found to be compatible. Sequencing of *SEMA7A* revealed a homozygous substitution, c.556G>A (p.Glu186Lys, rs572867366) and two silent polymorphisms c.507C>T (p.Tyr169Tyr, rs2075589) and c.1545A>G (p.Gln515Gln, rs741761). Whereas the c.556G>A variant is only present in 2% of the Esan population (Nigeria) dataset of the 1KGP databank and was not observed in other populations, the variants giving rise to the two silent mutations were commonly observed, showing respective frequencies of 0.22 and 0.495 averaged over all populations.

The new antigen was designated the eighth antigen of the JMH blood group system (ISBT 026008) and called JMHA, with 'A' standing for 'Arabia' as the patient was from Qatar. The proposed allele name is *JMH*01.-08.*

System 030: RHAG, Kg (ISBT 030005)

The Kg antigen was first discovered in an investigation of a woman whose newborn had HDFN [40]. The molecular nature of the Kg antigen has remained a mystery for over 30 years. A monoclonal antibody to the Kg antigen and recombinant protein were developed that allowed for immunoprecipitation analysis [41]. Immunoprecipitates from the proposita's RBC ghosts were subjected to mass spectrometry analysis. Carrier candidates of the antigen were *RHD*, *RHCE* and *RHAG*. Whereas *RHD* and *RHCE* were normal, DNA sequence analysis showed a heterozygous SNV in the third exon of *RHAG*, with c.490A>C (p.Lys164Gln) in a Kg-positive sample. The candidate for the Kg antigen was molecularly isolated and confirmed to be a determinant of the Kg antigen by cell transfection and flow cytometry analyses. The Kg antigen and the genetic mutation were then screened for in 61,362 Japanese blood donors. Kg phenotyping further clarified that 0.22% of the Japanese population studied was positive for the Kg antigen.

In 2010, an *RHAG* c.490A>C homozygous individual of Japanese origin with an antibody against the high-prevalence antigen DSLK was reported [42]. Kg appears to be antithetical to DSLK; however, this has not been confirmed by cross-testing with anti-DSLK since this antibody is no longer available. Kg has been transferred from the 700 series antigen, previously 700045 'Katagiri' (Kg), into the RHAG system as RHAG5.

CHANGES TO BLOOD GROUP ALLELE TABLES

There were changes made to the names of blood group alleles in the VEL, RAPH, RHAG and CROM systems where a minus sign had previously occurred after the star sign. For example, the *VEL*-01* allele was renamed to *VEL*01N.01*, which is the predominant null allele. The *CROM*−01* was renamed to *CROM*01.-01*, which defines an allele differing from the reference allele by a variant that results in the loss of one of the high-prevalence antigens expressed by the reference and for which the antithetical low-prevalence antigen has not been reported. The allele for KDAS will be defined as *KN*01.10*, which makes

*KN*01.-09* obsolete (this latter indicated the loss of an antigen before the discovery of the antithetical antigen).

Finally, an overview of all currently known antigens can be found on the ISBT webpage (https://www.isbtweb.org/fileadmin/user_upload/Table_of_blood_group_antigens_within_systems_v10.0_30-JUN-2021.pdf). This list is supplemented by a table of 'obsolete antigens', which is also available on the WPs website.

CONCLUSION

This report described the registration of new blood group systems and new antigens into existing systems over the course of four business meetings. The ISBT now recognizes 378 antigens, of which 345 are clustered within 43 blood group systems. The remaining 33 still have an unknown genetic basis and remain classified in either the 200 collections or the 700 or 901 series, awaiting the resolution of their genetic background.

It is of note that advances in genomic, proteomic and cellular technologies are contributing to this current wave of discoveries. This is contributing to both de novo discoveries and resolving antigens previously listed in the ISBT 200, 700 and 901 series. In addition, genomics continues to reveal a further sub-layer of blood group alleles associated with altered blood group phenotypes.

The ongoing recognition of new blood group systems and antigens underscores the diverse and complex biology of the red cell membrane. The curation of blood group systems, antigens and associated alleles is of clinical significance to provide for accurate typing and reporting for both donors and patients in the transfusion and antenatal settings. The Working Party continues to update the blood group antigen tables and the allele nomenclature tables. These can be found on the ISBT website (http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/).

ACKNOWLEDGEMENTS

Since the last report, Dr. Masja de Haas resigned from the Working Party. We sincerely thank Masja for her many contributions over the years and for her ongoing support. New members Nick Gleadall, William Joseph Lane, Peter Ligthart, Barbera Veldhuisen and Christoph Weinstock were welcomed into the Working Party. Since May 2021, IT expert Harald Obergasser assists the Working Party in the administration and curation of the blood group allele tables, with his work being funded by the ISBT. L.C. is funded by the Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP). Q.C. is supported by the Jiangsu Province Medical Elite Program (ZDRCB2016010), Jiangsu Province Social Development Program (BE2015717) and Fifth Phase of the 333 Program of Jiangsu Province (2016-III-3344). W.A.F. is supported by the Intramural Research Program (project ID ZIC CL002128) of the NIH Clinical Center. In receipt of an educational and scientific consultation funding from Thermo Fisher Scientific. M.L.O. is a Wallenberg Clinical Scholar, supported by the Knut and Alice Wallenberg Foundation (grant no. 2020.0234), the Swedish Research Council (grant no. 2019–01683) and the Swedish Government and County Councils (grant no. ALFSKANE-446521). F.F.W. received funding from the European Union for the production of COVID-19 convalescent plasma (ESI grant no. 101021487 DE-CCP-North). C.A.H. is funded by the Australian Red Cross Blood Service and acknowledges the Australian Government that funds the Blood Service for the provision of blood, blood products and services to the Australian Community.

C.A.H. and C.G. wrote the manuscript. All authors critically reviewed, revised and commented on the manuscript. As members of the Working Party, all authors have contributed equally to the discussion and conclusions drawn in this paper. All authors approved the final version of the paper.

APPENDIX: CURRENT MEMBERS OF THE WORKING PARTY FOR RED CELL IMMUNOGENETICS AND BLOOD GROUP TERMINOLOGY (IN ALPHABETICAL ORDER ACCORDING TO FAMILY NAME)

Prof. Dr. Lilian Castilho (executive committee), University of Campinas/Hemocentro, Campinas, Brazil. castilho@unicamp.br

Dr. Qing Chen, Jiangsu Province Blood Center, Nanjing, Jiangsu, China. qngchen@gmail.com; chenqing90@yahoo.com

Dr. Frederik Banch Clausen, Department of Clinical Immunology, Laboratory of Blood Genetics, Copenhagen University Hospital, Denmark. frederik.banch.clausen@rh.regionh.dk

Dr. Gregory A. Denomme, Grifols Laboratory Solutions, San Marcos, TX, USA. gregory.denomme@grifols.com

Prof. Dr. Willy Albert Flegel, Department of Transfusion Medicine, NIH Clinical Center, National Institutes of Health, Bethesda, MD, USA. flegelwa@cc.nih.gov

Prof. Dr. Christoph Gassner (co-chair), Institute of Translational Medicine, Private University in the Principality of Liechtenstein, Triesen, Liechtenstein. c@c-gassner.bio, christoph.gassner@ufl.li

Dr. Nick Gleadall, Department of Haematology, University of Cambridge and NHS Blood and Transplant, Cambridge Biomedical Campus, Cambridge, United Kingdom. ng384@medschl.cam.ac.uk

Dr. Åsa Hellberg, Department of Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, Sweden. asa.hellberg@med.lu.se

Prof. Dr. Catherine A. Hyland (co-chair), Australian Red Cross Lifeblood, Brisbane, Australia. chyland@arcbs.redcross.org.au

Dr. Yanli Ji, Institute of Clinical Blood Transfusion Guangzhou Blood Center, Guangzhou, People’s Republic of China. jiyanli2013@163.com

Dr. Margaret A. Keller (secretary), American Red Cross Blood Services, Philadelphia, USA. margaret.keller@redcross.org

Prof. Dr. William J. Lane, Department of Pathology, Brigham and Women’s Hospital, and Harvard Medical School, Boston, MA, USA. wlane@bwh.harvard.edu

Mr. Peter Ligthart, Department of Diagnostic Immunohematology, Sanquin, Amsterdam, The Netherlands. p.ligthart@sanquin.nl

Ms. Christine Lomas-Francis, Laboratory of Immunohematology and Genomics, New York Blood Center Enterprise, New York, New York, USA. clomas-francis@nybc.org

Dr. Nuria Nogues, Banc de Sang i Teixits, Barcelona, Spain. nnogues@bst.cat

Prof. Dr. Martin L. Olsson, Department of Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, Sweden. Department of Laboratory Medicine, Division of Hematology and Transfusion Medicine, Lund University, Lund, Sweden. martin_l.olsson@med.lu.se

Dr. Thierry Peyrard (treasurer), Etablissement Français du Sang Ile-de-France, Centre National de Référence pour les Groupes sanguins; UMR_S1134 Inserm Université Paris Cité, Paris, France. thierry.peyrard@efs.sante.fr; tpeyrard@ints.fr

Prof. Dr. Jill R. Storry (past chair), Department of Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, Sweden. Department of Laboratory Medicine, Division of Hematology and Transfusion Medicine, Lund University, Lund, Sweden. jill.storry@med.lu.se

Dr. Yoshihiko Tani, Osaka Red Cross Blood Center, Osaka, Japan. tani@osaka.bc.jrc.or.jp

MSc. Nicole Thornton, International Blood Group Reference Laboratory, NHS Blood and Transplant, Bristol, UK. nicole.thornton@nhsbt.nhs.uk

Prof. Dr. Ellen van der Schoot, Department of Experimental Immunohematology, Sanquin, Amsterdam, The Netherlands. e.vanderschoot@sanquin.nl

Dr. Barbera Veldhuisen, Department of Diagnostic Immunohematology, Sanquin, Amsterdam, The Netherlands. Department of Experimental Immunohematology, Sanquin, Amsterdam, The Netherlands. b.veldhuisen@sanquin.nl

Dr. Franz Wagner, German Red Cross Blood Service NSTOB, Springe, Germany. MVZ Clementinenkrankenhaus, Springe, Germany. fwagner@bsd-nstob.de

Dr. Christof Weinstock, Department of Transfusion Medicine, Institute for Clinical Transfusion Medicine and Immunogenetics, German Red Cross Blood Service, Ulm, Germany. c.weinstock@blutspende.de

Dr. Silvano Wendel, Blood Bank, Hospital Sirio-Libanes, São Paulo, Brazil. snwendel@terra.com.br

Dr. Connie Westhoff, Laboratory of Immunohematology and Genomics, New York Blood Center Enterprise, New York, New York, USA. cwesthoff@nybloodcenter.org

Dr. Vered Yahalom, Rabin Medical Center, Petach Tiqva and Sackler Faculty of Medicine, Tel Aviv University, Israel. veredya2@clalit.org.il; vered.yahalom@gmail.com

REFERENCES

1. Storry JR, Clausen FB, Castilho L, Chen Q, Daniels G, Denomme G, et al. International Society of Blood Transfusion Working Party on Red Cell Immunogenetics and Blood Group Terminology: report of the Dubai, Copenhagen and Toronto meetings. Vox Sang. 2019;114:95–102. [PubMed: 30421425]

2. ISBT Terminology Committee. Red cell immunogenetics and blood group terminology. [cited 2022 Aug 8]. Available from http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/

3. Kawabata K, Uchikawa M, Ohto H, Yasuda H, Tsuneyama H, Tsuchida H, et al. Anti-KANNO: a novel alloantibody against a red cell antigen of high frequency. Transfus Med Rev. 2014;28:23–8. [PubMed: 24485899]

4. Omae Y, Ito S, Takeuchi M, Isa K, Ogasawara K, Kawabata K, et al. Integrative genome analysis identified the KANNO blood group antigen as prion protein. Transfusion. 2019;59:2429–35. [PubMed: 31020675]

5. Stenfelt L, Hellberg Å, Möller M, Thornton N, Larson G, Olsson ML. Missense mutations in the C-terminal portion of the B4GALNT2-encoded glycosyltransferase underlying the Sd(a−) phenotype. Biochem Biophys Rep. 2019;19:100659. [PubMed: 31367682]

6. Veldhuisen B, Ligthart P, van der Mark-Zoet J, Javadi A, Tissoudali A, Dengerink I, et al. Identification of a single homozygous mutation in the B4GALNT2 gene in individuals lacking the Sd(a) (SID) antigen on red blood cells. Vox Sang. 2019;114:193.

7. Stenfelt L, Nilsson J, Hellberg Å, Liew YW, Morrison J, Larson G, et al. Glycoproteomic and phenotypic elucidation of B4GALNT2 expression variants in the SID histo-blood group system. Int J Mol Sci. 2022;23:3936. [PubMed: 35409292]

8. Cartron JP, Prou O, Luilier M, Soulier JP. Susceptibility to invasion by *Plasmodium falciparum* of some human erythrocytes carrying rare blood group antigens. Br J Haematol. 1983;55:639–47. [PubMed: 6200133]

9. Serafini-Cessi F, Monti A, Cavallone D. N-Glycans carried by Tamm-Horsfall glycoprotein have a crucial role in the defense against urinary tract diseases. Glycoconj J. 2005;22:383–94. [PubMed: 16622944]

10. Heaton BE, Kennedy EM, Dumm RE, Harding AT, Sacco MT, Sachs D, et al. A CRISPR activation screen identifies a pan-avian influenza virus inhibitory host factor. Cell Rep. 2017;20:1503–12. [PubMed: 28813663]

11. Renton PH, Howell P, Ikin EW, Giles CM, Goldsmith DKLG. Anti-Sda, a new blood group antibody. Vox Sang. 1967;13:493–501.

12. Vrignaud C, Mikdar M, Koehl B, Nair TS, Yang L, Laiguillon G, et al. Alloantibodies directed to the SLC44A2 CTL2 transporter define two new red cell antigens and a novel human blood group system. Transfusion. 2019;59:18A (Abstract).

13. Azouzi S, Mikdar M, Hermand P, Gautier EF, Salnot V, Willemetz A, et al. Lack of the multidrug transporter MRP4/ABCC4 defines the PEL-negative blood group and impairs platelet aggregation. Blood. 2020;135:441–8. [PubMed: 31826245]

14. Daniels GL, Simard H, Goldman M, Taliano V, Fleury M, Decary F, et al. PEL, a 'new' high-frequency red cell surface antigen. Vox Sang. 1996;70:31–3. [PubMed: 8928488]

15. Thornton N, Karamatic Crew V, Tilley L, Green CA, Tay CL, Griffiths RE, et al. Disruption of the tumour-associated EMP3 enhances erythroid proliferation and causes the MAM-negative phenotype. Nat Commun. 2020;11:3569. [PubMed: 32678083]

16. Duval R, Nicolas G, Willemetz A, Murakami Y, Mikdar M, Vrignaud C, et al. Inherited glycosylphosphatidylinositol defects cause the rare Emm-negative blood phenotype and developmental disorders. Blood. 2021;137:3660–9. [PubMed: 33763700]

17. Lane WJ, Aeschlimann J, Vege S, Lomas-Francis C, Burgos A, Mah HH, et al. PIGG defines the Emm blood group system. Sci Rep. 2021;11:18545. [PubMed: 34535746]

18. Daniels GL, Taliano V, Klein MT, McCreary J. Emm. A red cell antigen of very high frequency. Transfusion. 1987;27:319–21. [PubMed: 3603660]

19. Makrythanasis P, Kato M, Zaki MS, Saitsu H, Nakamura K, Santoni FA, et al. Pathogenic variants in PIGG cause intellectual disability with seizures and hypotonia. Am J Hum Genet. 2016;98:615–26. [PubMed: 26996948]

20. Sugier H, Vrignaud C, Duval R, Le Van Kim C, Arnoni C, Vendrame T, et al. Null allele of ABCC1 encoding the mulidrug resistance protein 1 defines a novel human blood group system. Vox Sang. 2020;115:40–1.

21. Flegel WA, Srivastava K, Sissung TM, Goldspiel BR, Figg WD. Pharmacogenomics with red cells: a model to study protein variants of drug transporter genes. Vox Sang. 2021;116:141–54. [PubMed: 32996603]
22. Zelinski T, Coghlan G, Liu XQ, Reid ME. ABCG2 null alleles define the Jr(a-) blood group phenotype. Nat Genet. 2012;44:131–2. [PubMed: 22246507]
23. Saison C, Helias V, Peyrard T, Merad L, Cartron JP, Arnaud L. The ABCB6 mutation p.Arg192Trp is a recessive mutation causing the Lan-blood type. Vox Sang. 2013;104:159–65. [PubMed: 22958180]
24. Helias V, Saison C, Ballif BA, Peyrard T, Takahashi J, Takahashi H, et al. ABCB6 is dispensable for erythropoiesis and specifies the new blood group system Langereis. Nat Genet. 2012;44:170–3. [PubMed: 22246506]
25. Ito S, Kaito S, Miyazaki T, Kikuchi G, Isa K, Tsuneyama H, et al. A new antigen SUMI carried on glycophorin A encoded by the GYPA*M with c.91A>C (p.Thr31Pro) belongs to the MNS blood group system. Transfusion. 2020;60:1287–93. [PubMed: 32358867]
26. Karamatic Crew V, Mayer B, Baglow L, Yürek S, Bartolmäs T, Walser P, et al. A novel high frequency antigen in the Lutheran blood group system (LUNU). Vox Sang. 2019;114:52.
27. Yosephi L, Karamatic Crew V, Shinar E, Zelig O, Yahalom V, Benjamin J, et al. A Lutheran related antibody detected in a patient with a homozygous missense BCAM mutation indicating a novel antigen of the system. Vox Sang. 2019;114:52.
28. Scharberg EA, Sturtzel A, Rothenberger-Murb S, Zimmermann B, Enkel S, Rink G, et al. A new low prevalence Diego blood group antigen found in a Caucasian blood donor. Vox Sang. 2021;116:29.
29. Srivastava K, Albasri J, Alsuhaibani OM, Aljasem HA, Bueno MU, Antonacci T, et al. SCAR: the high-prevalence antigen 013.008 in the Scianna blood group system. Transfusion. 2021;61:246–54. [PubMed: 33098316]
30. Flegel WA, Chen Q, Reid ME, Martin J, Orsini LA, Poole J, et al. SCER and SCAN: two novel high-prevalence antigens in the Scianna blood group system. Transfusion. 2005;45:1940–4. [PubMed: 16371048]
31. Hoffman R, Burgos A, Vail K, Lomas-Francis C, Vege S, Cusiek R, et al. A decade long search finds a new high prevalence antigen in the Sc system. Transfusion. 2021;60:7A–260A.
32. Lomas-Francis C, Tahiri T, Vege S, Shakarian G, Pailloz E, Ianosi-Irimie M, et al. GECT: a new high-prevalence antigen in the GE blood group system in a SCD patient with an apparent anti-GE2. Transfusion. 2020;60:7A–260A. [PubMed: 31469438]
33. Shakarian G, Ong J, Vege S, Lomas-Francis C, Jacquot C, Shaikh S, et al. A new antibody in the Gerbich Blood System against a novel high prevalence antigen named GEAR. Transfusion. 2021;60:7A–260A.
34. Moulds JM. The Knops blood-group system: a review. Immunohematology. 2010;26:2–7. [PubMed: 20795311]
35. Scharberg EA, Rink G, Schulz D, Rothenberger S, Stürtzel A, Gillhuber N, et al. KDAS, a new blood group antigen in the Knops blood group system antithetical to KCAM. Transfusion. 2020;60:E25–e7. [PubMed: 32589271]
36. Grueger D, Zeretzke A, Habicht CP, Skaik Y, Wagner FF, Scharberg EA, et al. Two novel antithetical KN blood group antigens may contribute to more than a quarter of all KN antisera in Europe. Transfusion. 2020;60:2408–18. [PubMed: 32870515]
37. Vrignaud C, Ramelet S, Herb A, Raneri A, Khalloufi M, Laiguillon G, et al. Characterization of a novel high-prevalence antigen in the JMH blood group system. Vox Sang. 2019;114:52–3.
38. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, et al. A global reference for human genetic variation. Nature. 2015;526:68–74. [PubMed: 26432245]
39. Henny C, Thornton N, Laundy R, Borowski A, Stettler J, Lejon Crottet S, et al. An antibody against a novel high prevalence antigen in the JMH blood group system. Vox Sang. 2020;115:231.
40. Ichikawa Y, Sato C, McCreary J, Lubenko A. Kg, a new low-frequency red cell antigen responsible for hemolytic disease of the newborn. Vox Sang. 1989;56:98–100. [PubMed: 2501936]

41. Tanaka M, Abe T, Minamitani T, Akiba H, Horikawa T, Tobita R, et al. The Kg-antigen, RhAG with a Lys164Gln mutation, gives rise to haemolytic disease of the newborn. Br J Haematol. 2020;191:920–6. [PubMed: 32705675]

42. Tilley L, Green C, Poole J, Gaskell A, Ridgwell K, Burton NM, et al. A new blood group system, RHAG: three antigens resulting from amino acid substitutions in the Rh-associated glycoprotein. Vox Sang. 2010;98:151–9. [PubMed: 19744193]

Highlights

- The ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology (WP for RCI and BGT) held four business meetings between June 2019 and June 2021 to consider the evidence for ratifying and naming new blood group systems and antigens.
- Seven new blood group systems, KANNO, SID, CTL2, PEL, MAM, EMM and ABCC1, were ratified, and a further 15 antigens added to existing systems: a total of 43 blood group systems comprising 345 antigens are now registered on the ISBT website.
- Significance: The curation of tables for blood group systems, antigens and associated alleles is of clinical significance for accurate typing, and the ISBT WP RCI and BGT members continue to maintain these tables on the ISBT website (https://www.isbtweb.org/isbt-working-parties/rcibgt.html).

TABLE 1

New blood group systems registered by the Working Party at business meetings conducted in Basel in June 2019 and over the first virtual meeting in September 2020 and the second virtual meeting in December 2020

Business meeting	ISBT number	Blood group system	Gene name and alternative name	Reference sequence	Antigens	Reference
Basel	037	KANNO	*PRNP* *CD230*	NG_009087.1	KANNO1	[4]
Basel	038	SID	*B4GALNT2* *GALGT2*	AJ517770 and AJ517771	Sd[a]	[5]
Basel and first virtual	039	CTL2	*CTL2* *SLC44A2*	NC_000019.10 (KM024996)	VER and RIF	[12]
First virtual	040	PEL	*ABCC4* *MOAT-B*	NG_050651 (LRG 1183)	PEL	[13]
First virtual	041	MAM	*EMP3* *YMP*	(NC_000019.10)	MAM	[15]
Second virtual	042	EMM	*PIGG* *GPI7*	NG_051621.1	Emm	[16, 17]
Second virtual	043	ABCC1	*ABC29*	NG_028268.2	WLF	[20]

Note: *B4GALNT2* has a short and a long form; hence there are two reference sequences. AJ51770 is 60 amino acids longer than AJ517771 due to the differential use of two alternative exons 1. *GALGT2* has been used as an alternative name for *B4GALNT2*.

TABLE 2

New antigens added to pre-existing blood group systems by the Working Party: Reported at the business meeting in Basel in June 2019, the second virtual business meeting in December 2020 and the third virtual business meeting in June 2021

Business meeting	ISBT number	Blood group system	Antigen number	Alt. name	Antigen prevalence	Allele name	Molecular basis	Protein change	SNV (rs-number)	GenBank	Reference
Second virtual	ISBT 002	MNS	MNS50	SUMI	Low	*GYPA*50*	*GYPA c.91A>C*	GPA p.Thr31Pro	Pending	LC495310	[25]
Third virtual	ISBT 004	RH	RH63	CETW	Low	To be determined	*RHCE c.486C>G*	RhCE p.Asn162Lys	rs199725473	MZ326705	Manuscript in preparation
Basel	ISBT 005	LU	LU28	LUNU	High	*LU*02.-28*	*BCAM c.121G>A*	BCAM p.Val41Met	rs957795435	MK965667	[26]
Basel	ISBT 005	LU	LU29	LURA	High	*LU*02.-29*	*BCAM c.1351A>C*	BCAM p.Lys451Gln	rs28399630	Pending	[27]
Third virtual	ISBT 010	DI	DI23	DIST	Low	*DI*02.23*	*SLC4A1 c.1447G>A*	CD233 p.Gly483Ser	rs544557335	Pending	[28]
Second virtual	ISBT 013	SC	SC8	SCAR	High	*SC*01.-08*	*ERMAP c.424C>G*	ERMAP p.Gln142Glu	Pending	MK933825	[29]
Second virtual	ISBT 013	SC	SC9	SCAC	High	*SC*01.-09*	*ERMAP c.217C>T, c.219C>T*	ERMAP p.Arg73Cys p.Arg73Cys	rs149787850 rs33954154	MW427218	[31]
Second virtual	ISBT 020	GE	GE12	GECT	High	*GE*01.-13*	*GYPC c.59C>T*	GPC p.Pro20Leu	rs143216051	Pending	[32]
Second virtual	ISBT 020	GE	GE13	GEAR	High	*GE*01.-14*	*GYPC c.118G>A c.333A>C*	GPC p.Gly40Arg p.Gly111Gly	rs772372126 rs1050967	Pending	[33]
Basel	ISBT 022	KN	KN10	KDAS	Average	*KN*01.10*	*CR1 c.4843A>G*	CR1 p.Ile1615Val	rs6691117	Pending	[35]
Second virtual	ISBT 022	KN	KN11	DACY	Average	*KN*01*	*CR1 c.3623A*	CR1 p.His1208	rs2274567	Pending	[36]
Second virtual	ISBT 022	KN	KN12	YCAD	Average	*KN*01.12*	*CR1 c.3623A>G*	CR1 p.His1208Arg	rs 2274567	Pending	[36]
Basel	ISBT 026	JMH	JMH7	JMHN	High	*JMH*01.-07*	*SEMA7A c.709G>A c.1545A>G c.1865G>A*	CD108 p.Asp237Asn p.Gln515Gln p.Arg622His	rs140707085 rs741761 rs140128092	Pending	[37]
Second virtual	ISBT 026	JMH	JMH8	JMHA	High	*JMH*01.-08*	*SEMA7A c.507C>T c.556G>A c.1545A>G*	CD108 p.Tyr169Tyr p.Glu186Lys p.Gln515Gln	rs2075589 rs572867366 rs741761	MT017654	[39]

Business meeting	ISBT number	Blood group system	Antigen number	Alt. name	Antigen prevalence	Allele name	Molecular basis	Protein change	SNV (rs-number)	GenBank	Reference
Second virtual	ISBT 030	RHAG	RHAG5	Kg	Low	*RHAG*01.-03*	*RHAG c.490A>C*	RhAG p.Lys164Gln	rs144305805	LC508243	[41]

Abbreviations: GPA, glycophorin A; GPC, glycophorin C; SNV, single nucleotide variant.