REVIEW ARTICLE

Blood group systems and antigens described in the last 20 years: an update

Natalya J Clark and Holly E Perry

ABSTRACT

Objectives: New information about blood group systems and antigens appears frequently but has not been recently collated as a single text. Books such as the *Blood Group Antigen FactsBook* by Reid, Lomas-Francis and Olsson provide an excellent reference source. However, the last edition was released a decade ago, and much has been discovered since then. New information is used to review requirements for red cell antibody screening cells, maintain rare donor databases, monitor clinical events and educate practitioners. The aim of this study was to summarise information elucidated in the past 20 years, with emphasis on significance in clinical practice. We aimed to provide a resource that may be useful to practising transfusion scientists.

Methods: Information was gathered by literature search.

Results: 122 blood group antigens and 17 blood group systems were described in the past 20 years (2003 – 2023). 31 antibodies were either implicated in transfusion reactions or haemolytic disease of the fetus and newborn or were considered to have the potential to cause these events.

Conclusion: Discovery and elucidation of blood group systems continues. Due to the rarity of clinical events, the clinical significance of many of the newer antigens and antibodies described is not yet certain. Nevertheless, it is important for transfusion scientists to be aware of new blood groups and monitor the likelihood of antibodies to cause transfusion reactions and/or haemolytic disease of the fetus and newborn. This literature review provides an update for transfusion scientists.

Key words: Blood group antigen, Rare blood group antibodies

NZ J Med Lab Sci 2024; 78(1): 06:19

INTRODUCTION

Blood group antigens are inherited markers found on surfaces including the red blood cell membrane. Corresponding antibodies can have a range of clinical effects, including haemolytic transfusion reactions (HTR), haemolytic disease of the fetus and newborn (HDFN) and autoimmune haemolytic anaemia (AIHA).

The International Society of Blood Transfusion (ISBT) classifies all known blood group systems and antigens. It defines a blood group system as a genetically discrete system of "one or more blood group antigens that are related by one gene, or one complex of two or more closely linked genes that are homologous" (1). A homolog is a gene that has a very similar nucleotide sequence to another gene.

There are several blood group antigens that cannot currently be classified as a system based on ISBT requirements. These form the 700 series (low prevalence antigens found at a population frequency of <1%), the 901 series (high prevalence antigens found at a population frequency of >90%) and independent collections which contain antigens that are related, but not yet fully elucidated at a genetic level (1).

Blood group systems frequently arise from an ancestral gene coding for a protein on the red cell surface, and polymorphisms are the result of single nucleotide changes. For example, in the Duffy system, the gene is FY and the reference allele is FY*02 (Fy^b), which encodes 4 antigens on the Duffy glycoprotein, a receptor for chemokines. FY*01 (Fy^a) arises from a change at nucleotide 125, producing an amino acid (aa) change at aa42 (2). Single nucleotide polymorphisms (SNP) are responsible for most of the variation in blood groups.

Hybrid genes are responsible for the high degree of these polymorphism seen in the Rh and MNS blood group systems. These genetic variants occur at different frequencies around the world due to both selective pressures and geographic isolation. Null phenotypes (where no blood group structure in a system is present on the red cell) may be associated with a survival advantage. For example, Duffy null provides protection against some species of malaria; lacking the Duffy glycoprotein on the cell surface removes the ability of the parasite to bind and invade the red cell (2). Consequently, Duffy null is rare in countries where malarial parasites are absent, but common in malaria-endemic countries (3).

Advances in molecular technology in the past 20 years have greatly assisted the modern description of blood groups and allow classification of systems and antigens based on their exact genetic basis. As of December 2023, there were 49 genes determining 45 blood group systems and 360 blood group antigens, as well as 33 blood group antigens that have not yet been classified into a blood group system (1). Of these, 17 blood group systems and 122 blood group antigens were discovered in the last 20 years (2003 – 2023).

This report provides an update on the blood group antigens that have been described in the last 20 years, including genetic basis of variants and the clinical significance of their antibodies where known.

MATERIAL AND METHODS

A rigorous systematic literature search of the Wiley Online Library was performed, focusing on three journals: *Vox Sanguinis*, *Transfusion* and *Transfusion Medicine*. Information was also gathered from the Blood Group Antigens FactsBook (3rd ed.) and the Genome Aggregation Database (gnomAD) (4). ISBT nomenclature was used.

Data is presented in two sections: additions to systems and new systems. Data is tabulated throughout, with the column "clinical significance" referring to the reported potential of the antibody to the antigen described to cause haemolysis. The word "new" refers to antigens or systems described since 2003. Although some antigens described have been known for many years, the "year described" in tables refers to the year the antigen was fully elucidated at a genetic level. Where antigen frequencies are known to differ in different regions, more than one frequency is provided. When a single figure is given, it is assumed that antigen frequency is similar across many populations (4).

RESULTS

122 blood group antigens and 17 blood group systems were described in the past 20 years (2003 – 2023). Of these, the following have antibodies that are either clinically significant, or potentially clinically significant but infrequent: ENEV (MNS45), SARA (MNS47), P^k (P1PK3), CETW (RH63), VONG (KEL28), KEAL (KEL39), KHOZ (KEL41), DISK (DI22), YTGT (YT6), SCAN (SC7), SCAC (SC9), DOMR (DO7), GECT (GE13), INFI (IN3), PX2 (GLOB4), DSLK (RHAG3), Kg (RHAG5), THIN (RHAG7), Jr^a (JR1), Lan (LAN1), Vel (VEL1), At^a (AUG2), ATML (AUG3), ATAM (AUG4), Sd^a (SID1), MAM (MAM1), Emm (EMM1), Er3 (ER3), ERSA (ER4), ERAMA (ER5) and CD36.1. Anti-Kg, anti-Jr^a, anti-Lan, anti-Vel, anti-At^a and Anti-Sd^a were clinically significant antibodies seen in multiple clinical cases. These six antibodies were discovered more than 20 years ago, but the respective blood group systems were fully elucidated more recently.

Section 1. Additions to Blood Group Systems

002 - MNS

Table 1. New antigens in the MNS system (5-12)

Name	#	Year Described	Antigen frequency	Clinical significance
ENDA	44	2008	>99%	Unknown
ENEV	45	2010	>99%	Mild HTR
MNTD	46	2006	<1%	Unknown
SARA	47	2014	<1%	Severe HDFN
KIPP	48	2015	<1%	Unknown
JENU	49	2016	Most populations >99% Less frequent in Southeast Asians	Unknown
SUMI	50	2020	<1%	Unlikely

ENDA, KIPP and JENU are the result of hybrids between Glycophorin A (GYPA) and Glycophorin B (GYPB), while ENEV, MNTD, SARA and SUMI are the result of SNPs. One antithetical pair of antigens was discovered: ENDA with DANE (MNS32, previously described).

One antigen, SARA, was previously assigned 700.052, and moved to the MNS blood group system when its genetic basis was identified. It is a low prevalence antigen found in one Australian and one Canadian family, and its antibody has caused severe HDFN in one newborn (9).

003 - P1PK

Table 2. New antigens in the P1PK system (2, 13-14)

Name	#	Year Described	Antigen frequency	Clinical significance
P^k	3	2010	>99%	Probable
NOR	4	2012	<1%	Unknown

The P1PK system was renamed from P after the P and P^k antigens were found to be tied to the same gene - Alpha 1,4-Galactosyltransferase (*A4GALT*), which is found on 22q13.2 chromosome (2). During this change, P^k (P1PK3) was moved from the now obsolete Globoside collection into the P1PK system. Globoside is now a blood group system in its own right. (system 028, Table 18).

P^k (previously 209.002) is only expressed strongly on the cells of P_1^k and P_2^k individuals (2). Inactivating mutations in the B3GALNT1 gene cause an increase in expression of P^k. Rare inactivating mutations in *A4GALT* lead to the P^k negative null phenotype (p). Anti-P^k is usually found alongside anti-P and anti-P1 (anti-PP1P^k), which can cause severe transfusion reactions, spontaneous abortions and HDFN (2).

004 - Rh

Table 3. New antigens in the Rh system (15-22)

Name	#	Year Described	Antigen frequency	Clinical significance
CENR	56	2004	<1%	Unknown
CEST	57	2009	>99%	Unknown
CELO	58	2011	>99%	Unknown
CEAG	59	2015	>99%	Unknown
PARG	60	2017	<1%	Unknown
CEVF	61	2013	<1%	Unknown
CEWA	62	2012	>99%	Unknown
CETW	63	2021	<1%	HDFN

CENR, CEST, CELO, CEAG, PARG and CEVF are caused by hybrid RHCE alleles, while CEWA and CETW are the result of SNPs in *RHCE*. Two antithetical pairs of antigens were discovered: CEST and JAL (RH48), and CELO and Crawford (RH43).

Of the eight antigens recently assigned to the Rh blood group system, only CETW is known to be clinically significant, having caused HDFN in one indigenous Australian newborn (22).

005 - Lutheran

Table 4. New antigens in the Lutheran system (23-30)

Name	#	Year Described	Antigen frequency	Clinical significance
LURC	22	2009	>99%	Unknown
LUIT	23	2023	>99%	Unknown
LUGA	24	2023	>99%	Unknown
LUAC	25	2016	>99%	Unknown
LUBI	26	2016	>99%	Unknown
LUYA	27	2018	>99%	Unknown
LUNU	28	2019	>99%	Unknown
LURA	29	2019	>99%	Unknown
LUOM	30	2023	>99%	Unknown

All new antigens in the Lutheran blood group system are the result of SNPs in Basal Cell Adhesion Molecule (*BCAM).*

LUAC has some relevance to New Zealand, as its antibody was found in a Māori patient in Auckland (26). Its clinical significance is unknown.

006 - Kell

Table 5. New antigens in the Kell system (31-43)

Name	#	Year Described	Antigen frequency	Clinical significance
VONG	28	2003	<1%	Mild HDFN
KALT	29	2006	>99%	Unknown
KTIM	30	2006	>99%	Unknown
KYO	31	2006	Most populations <1% Japanese 1.5%	Unknown
KUCI	32	2013	>99%	Unknown
KANT	33	2013	>99%	Unknown
KASH	34	2010	>99%	Unknown
KELP	35	2010	>99%	Unknown
KETI	36	2011	>99%	Unknown
KHUL	37	2011	>99%	Unknown
KYOR	38	2012	<1%	Unknown
KEAL	39	2016	<1%	Severe HDFN
KHIZ	40	2022	>99%	Unknown
KHOZ	41	2022	<1%	HTR

All new antigens in the Kell blood group system are the result of SNPs in Kell metallo-endopeptidase (*KEL*); KELP is unique in that it is a result of two separate SNPs in *KEL*. Four pairs of antithetical antigens have been identified; VONG with VLAN (KEL25, previously identified), KYO with KYOR, KHUL with KEAL, and KHIZ with KHOZ.

010 - Diego

Table 6 New antigens in the Diego system (44,45)

Name	#	Year Described	Antigen frequency	Clinical significance
DISK	22	2010	>99%	Probable
DIST	23	2021	<1%	Unknown

Both new antigens in the Diego blood group system are the result of SNPs in Solute Carrier Family 4 Member 1 (*SLC4A1*). DISK is antithetical to Wu (DI9). Anti-DISK was found in an Irish proband after she miscarried, but its clinical relevance to the miscarriage was uncertain (44).

011 - Yt

Table 7. New antigens in the Yt system (46-48)

Name	#	Year Described	Antigen frequency	Clinical significance
YTEG	3	2017	>99%	Unknown
YTLI	4	2018	>99%	Unknown
YTOT	5	2018	>99%	Unknown
YTGT	6	2022	>99%	HTR

All new antigens in the Yt blood group system are the result of SNPs in *acetylcholinesterase (ACHE)*. Anti-YTGT was found in two unrelated Native American patients, one of whom experienced an acute HTR following transfusion (48).

013 - Scianna

Table 8 New antigens in the Scianna system (49-52)

Name	#	Year Described	Antigen frequency	Clinical significance
STAR	5	2005	>99%	Unknown
SCER	6	2005	>99%	Unknown
SCAN	7	2005	>99%	HTR
SCAR	8	2020	>99%	Unknown
SCAC	9	2022	>99%	Probable

All new antigens in the Scianna blood group system are the result of SNPs in Erythroblast Membrane Associated Protein (*ERMAP*).

In vitro tests suggest anti-SCAR is unlikely to be clinically significant, and there was no evidence of haemolysis after one SCAR negative proband received an antigen mismatched transfusion (51). However, the patient was receiving hydroxyurea at the time and may have otherwise developed anti-SCAR at high enough titres to be clinically significant.

014 - Dombrock

Table 9. New antigens in the Dombrock system (53-57)

Name	#	Year Described	Antigen frequency	Clinical significance
DOYA	6	2010	>99%	Unknown
DOMR	7	2010	>99%	Possible HDFN
DOLG	8	2011	>99%	Unknown
DOLC	9	2013	>99%	Unknown
DODE	10	2015	>99%	Unknown

All new antigens in the Dombrock blood group system are the result of SNPs in ADP-Ribosyltransferase 4 (*ART4*); DOMR is the result of two SNPs in *ART4*. Anti-DOMR caused a positive DAT, jaundice and reticulocytosis in a newborn (54).

015 - Colton

Table 10. New antigens in the Colton system (58)

Name	#	Year Described	Antigen frequency	Clinical significance
Co4	4	2010	>99%	Unknown

Co4 is the result of a SNP in Aquaporin 1 (*AQP1*).

016 - Landsteiner-Wiener

Table 11. New antigens in the Landsteiner-Wiener system (59)

Name	#	Year Described	Antigen frequency	Clinical significance
LWEM	8	2022	>99%	Unknown

LWEM is the result of a SNP in Intercellular Adhesion Molecule-4 (*ICAM4*).

020 - Gerbich

Table 12. New antigens in the Gerbich system (60-63)

Name	#	Year Described	Antigen frequency	Clinical significance
GEIS	9	2004	<1%	Unknown
GEPL	10	2008	>99%	Unknown
GEAT	11	2008	>99%	Unknown
GETI	12	2008	>99%	Unknown
GECT	13	2020	>99%	HTR
GEAR	14	2016	>99%	Unknown

All antigens in the Gerbich blood group system are the result of SNPs in Glycophorin C (*GYPC*).

021 - Cromer

Table 13. New antigens in the Cromer system (64-71)

Name	#	Year Described	Antigen frequency	Clinical significance
SERF	12	2004	>99%	Unknown
ZENA	13	2007	>99%	Unknown
CROV	14	2007	>99%	Unknown
CRAM	15	2007	>99%	Unknown
CROZ	16	2010	>99%	Unknown
CRUE	17	2012	>99%	Unknown
CRAG	18	2012	>99%	Unknown
CROK	19	2012	>99%	Unknown
CORS	20	2020	>99%	Unknown

All new antigens in the Cromer blood group system are the result of SNPs in Decay accelerating factor (*DAF)*. Anti-CRUE was found in Auckland in a Thai patient (68)

022 - Knops

Table 14. New antigens in the Knops system (72-76)

Name	#	Year Described	Antigen frequency	Clinical significance
KCAM	9	2005	Caucasians 98% West Africans 20%	Unknown
KDAS	10	2020	Europeans 39% Africans 95.8% South Asians 67.7%	Unknown
DACY	11	2020	Europeans 96% Africans 95% South Asians 82%	Unknown
YCAD	12	2020	Europeans 35% Africans 40% South Asians 67%	Unknown
KNMB	13	2023	>99%	Unknown

All new antigens in the Knops blood group system are caused by SNPs in Complement Component (3b/4b) Receptor 1 (*CR1*). KCAM and KDAS are antithetical antigens, as are DACY and YCAD.

023 - Indian

Table 15 New antigens in the Indian system (77-79)

Name	#	Year Described	Antigen frequency	Clinical significance
INFI	3	2007	>99%	Mild HDFN
INJA	4	2007	>99%	Unknown
INRA	5	2016	>99%	Unknown
INSL	6	2018	>99%	Unlikely

All new antigens in the Indian blood group system are caused by SNPs in *CD44.*

024 - OK

Table 16. New antigens in the OK system (80,81)

Name	#	Year Described	Antigen frequency	Clinical significance
OKGV	2	2003	>99%	Unknown
OKVM	3	2006	>99%	Unknown

Both new antigens in the OK blood group system are caused by SNPs in Basigin (*BSG*).

026 - John Milton Hagen

Table 17. New antigens in the John Milton Hagen system (82-86)

Name	#	Year Described	Antigen frequency	Clinical significance
JMHK	2	2006	>99%	Unknown
JMHL	3	2006	>99%	Unknown
JMHG	4	2006	>99%	Unknown
JMHM	5	2006	>99%	Unknown
JMHQ	6	2010	>99%	Unknown
JMHN	7	2019	>99%	Unknown
JMHA	8	2020	>99%	Unlikely

All new antigens in the JMHK blood group system are the result of SNPs in Semaphorin 7A (*SEMA7A*).

Section 2. New Systems

028 – Globoside (promoted from a collection to a system in 2003).

In 2003 the system contained one antigen P but new antigens have subsequently been added (Table 18). The Globoside blood group system is encoded by Beta-1,3-N-Acetylgalactosaminyltransferase 1 (*B3GALNT1*), which is found on 3q26 chromosome (2). The gene encodes an enzyme which transfers *N*-acetylgalactosamine onto the P^k antigen in the P1PK system to form P.

Table 18. New antigens in the Globoside system (87,88)

Name	#	Year Described	Antigen frequency	Clinical significance
PX2	4	2011	>99%	Probable
ExtB	5	2019	Caucasians 13% African Americans 24% Asians 31%	Unknown

Anti-PX2 is found in patients with the very rare Pk phenotype. This phenotype arises from inactivations of the B3GALNT1 gene. Usually, anti-PX2 is found alongside other antibodies (anti-P, anti-P1) so its clinical significance is hard to determine. PX2 is abundant on p cells (PPIPk negative) so patients with anti-PX2 have an incompatible crossmatch with cells from p individuals. ExtB is associated with the B antigen. Anti-ExtB is found in group O individuals, as well as group AB and B Pk individuals, and reacts with B cells that are PPIPk-.

030 - Rh-Associated Glycoprotein (RHAG) (promoted to a system in 2008).

Antigens described since 2003 are listed in Table 19.

The RHAG blood group system is encoded by Rh-Associated Glycoprotein (*RHAG*), which is found on 6p21.3 chromosome (2). The gene encodes a multi-pass membrane glycoprotein which is associated with RhD, RhCE, GPB, LW and CD47. This complex of molecules helps to maintain erythrocyte membrane integrity. RHAG is also involved in transporting some molecules and cations across the red cell membrane. It is expressed only on RBCs, but RHAG homologs can be found in other tissues.

Table 19. New antigens in the RHAG system (89-95)

Name	#	Year Described	Antigen frequency	Clinical significance
DUCLOS	1	2010	>99%	Unknown
Ol^a	2	2010	<1%	Unknown
DSLK	3*	2010	>99%	Probable
Kg	5	2020	<1%	Severe HDFN Probable HTR
SHER	6	2022	<1%	Unknown
THIN	7†	2023	<1%	HDFN
* "Provisional number assigned awaiting further examples of the DSLK− phenotype to confirm the polymorphism." (1) † Provisional number assigned.				

All antigens in the RHAG blood group system are the result of SNPs in *RHAG*. One new pair of antithetical antigens were discovered: DSLK and Kg. Three of the antigens were identified more than 20 years ago but elucidated more recently: DUCLOS (previously 901.013), Ol^a (previously 700.043) and Kg (previously 700.045). Kg is present in approximately 0.2% of the Japanese population (90). Anti-Kg has caused two severe cases of HDFN that required exchange transfusion, and in vitro tests have suggested that it is capable of causing HTRs (90,93). In vitro tests suggest that the antibody to its antithetical antigen, DSLK, may also be clinically significant.

031 - FORS

The FORS blood group system is encoded by Globoside Alpha-1,3-N-Acetylgalactosaminyltransferase 1 (*GBGT1*), which is found on 9q34.2 chromosome (2). The gene encodes a glycosyltransferase, which catalyses the formation of Forssman glycolipids. These glycolipids are usually seen in animals and humans have corresponding naturally occurring antibodies.

Table 20. Antigens in the FORS system (96)

Name	#	Year Described	Antigen frequency	Clinical significance
FORS1	1	2013	<1%	Unknown

FORS1 is caused by a SNP in *GBGT1*.

032 - JR

The JR blood group system is encoded by ATP Binding Cassette Subfamily G Member 2 (*ABCG2*), which is found on 4q22.1 chromosome (97). The gene encodes an ATP-dependent transporter that can transport a wide specificity of substrates, particularly uric acid. It is expressed on a range of cells, including the placenta and epithelial cells.

Table 21. Antigens in the JR system (97-102)

Name	#	Year Described	Antigen frequency	Clinical significance
Jr^a	1	2012	>99%	Severe HDFN HTR

The null phenotype of Jr^a (previously 901.005) is caused by mutations in *ABCG2*. Jr(a-) has a prevalence of 0.03% in Japanese and <0.01% of most other populations. Anti-Jr^a is clinically significant, having caused severe and even fatal HDFN, and sometimes causes HTRs (98-102).

033 - LAN

The LAN blood group system is encoded by ATP-binding Cassette Subfamily B Member 6 (*ABCB6*), which is found on 2q36 chromosome (103). The gene encodes an ATP-dependent transport protein which transports heme and its precursors across the red blood cell membrane and outer mitochondrial membrane (104).

Table 22. New antigens in the LAN system (103,105)

Name	#	Year Described	Antigen frequency	Clinical significance
Lan	1	2012	>99%	Severe HDFN Probable HTR

The null phenotype of Lan (previously 901.002) is caused by inactivating mutations in *ABCB6*.

034 - Vel

The Vel blood group system is encoded by Small Integral Membrane Protein 1 (*SMIM1*), which is found on chromosome 1p36.32 (106). It encodes a transmembrane protein and is found in a range of tissues, particularly in the bone marrow, testes and kidney (107).

Table 23 Antigens in the Vel system (108-113)

Name	#	Year Described	Antigen frequency	Clinical significance
Vel	1	2013	>99%	HDFN Severe HTR AIHA

The null phenotype of Vel is caused by inactivating mutations in *SMIM1*. Anti-Vel is capable of causing AIHA, severe HTR and rarely HDFN (109-113).

035 - CD59

The CD59 blood group system is encoded by *CD59* which is found on 11p13 chromosome (114). The gene encodes a glycoprotein that has a role in complement regulation (inhibition of the MAC complex) (115). It is expressed on all blood cells, endothelial cells and epithelial cells. It is also present in tear fluid (116).

Table 24. Antigens in the CD59 system (117)

Name	#	Year Described	Antigen frequency	Clinical significance
CD59.1	1	2014	>99%	Unknown

Anti-CD59.1 was found in a patient with a CD59 deficiency. Very few cases of CD59 deficiency have been reported; seven as of 2014, and three distinct CD59-null alleles were implicated. Of several transfusions given to one proband, only one post-transfusion test revealed a transiently positive DAT with no clinical signs of HTR (117).

036 - Augustine

The Augustine blood group system is encoded by Solute Carrier Family 29 Member 1 (*SLC29A1*), which is found on 6p21.1 chromosome (118). The gene encodes the ENT1 protein, which may have a role in adenosine transport and erythroid differentiation, as well as being involved in regulating bone metabolism (119). This protein is found ubiquitously in human tissues.

Table 25. Antigens in the Augustine system (119-124)

Name	#	Year Described	Antigen frequency	Clinical significance
AUG1	1	2015	>99%	Unknown
At^a	2	2015	>99%	Moderate HDFN Severe HTR AIHA
ATML	3	2018	<1%	Severe HDFN
ATAM	4	2023	>99%	Probable

All antigens in the Augustine blood group system are the result of SNPs in *SLC29A1*, except for AUG1 whose loss is associated with the rare Augustine null phenotype. Anti-At^a has been found in a number of African American individuals. In vitro tests suggest that anti-At^a is clinically significant, and it has been implicated in cases of HDFN (one of which was moderate), HTRs (one of which was severe) and AIHA (120-122).

037 - KANNO

The KANNO blood group system is encoded by Prion Protein (*PRNP*), which is found on 20p13 chromosome (125). The gene encodes prion protein, a glycoprotein found in the brain and other tissues. It may have a role in copper transport and neuroprotection, as mutations are associated with Creutzfeldt-Jakob disease (126). Its function in RBCs is unknown

Table 26. Antigens in the KANNO system (125,127,128)

Name	#	Year Described	Antigen frequency	Clinical significance
KANNO1	1	2020	Most populations >99% Japanese 94.2% Southeast Asians 96%	Unknown

The clinical significance of anti-KANNO is unknown, but among 16 reported cases of pregnancy and 7 reported cases of transfusion there were no cases of HDFN or HTR, with only one newborn testing DAT positive (127).

038 - SID

The SID blood group system is encoded by Beta-1,4-N-Acetyl-Galactosaminyltransferase 2 (*B4GALNT2*), which is found on 17q21.32 chromosome (129). The gene encodes an enzyme which catalyses the formation of the carbohydrate determining the Sd^a antigen. This enzyme is absent on gastrointestinal cancer cells, suggesting it may play a role in eliminating metastasis. It is found in the kidney, colon and stomach, as well as human serum, milk, meconium and urine.

Table 27. Antigens in the SID system (130-133)

Name	#	Year Described	Antigen frequency	Clinical significance
Sd^a	1	2019	Most populations 91%	HTR

The loss of Sd^a is associated with mutations in the *B4GALNT2* gene. 91% of the population carries this antigen on red cells, but only 4% are Sd^a negative in all tissues and therefore capable of making anti-Sd^a (130). Anti-Sd^a can cause HTR, particularly when RBCs of the rare Cad (Sda++) phenotype are transfused, as these react more strongly with anti-Sd^a (132,133).

039 - CTL2

The CTL2 system is encoded by Solute Carrier Family 44 Member 2 (*SLC44A2*), which is found on 19p13.2 chromosome (134,135). The gene encodes the CTL2 glycoprotein, which has a role in choline transport and carries HNA-3 (human neutrophil antigen), the antibody of which causes severe and fatal transfusion-related acute lung injury (TRALI). CTL2 is found in a variety of tissues, notably blood cells, inner ear and lung endothelium (135).

Table 28. Antigens in the CTL2 system (136)

Name	#	Year Described	Antigen frequency	Clinical significance
VER	1	2019	>99%	Unknown
RIF	2	2019	>99%	Unknown

Anti-VER was found in one CTL2 null proband (136). RIF is the result of a SNP in *SLC44A2*.

040 - PEL

The PEL blood group system is encoded by ATP Binding Cassette Subfamily C Member 4 (*ABCC4*), which is found on 13q32.1 chromosome (137). The gene encodes an ATP-dependent transport protein which transports a variety of molecules and is involved in erythropoiesis (138). It is found in a variety of tissues, particularly the prostate and kidney (139).

Table 29. Antigens in the PEL system (140)

Name	#	Year Described	Antigen frequency	Clinical significance
PEL	1	2020	>99%	Unknown

The loss of PEL (previously 901.014) is caused by a deletion of *ABCC4*.

041 - MAM

The MAM blood group system is encoded by Epithelial Membrane Protein 3 (*EMP3*), which is found on 19q13.33 chromosome (141). The gene encodes the EMP3 protein, which has a role in tumour suppression (142). It is expressed in the ovary, rectum, liver, kidney and embryonic lung (142).

Table 30. Antigens in the MAM system (143,144)

Name	#	Year Described	Antigen frequency	Clinical significance
MAM	1	2020	>99%	Severe HDFN Probable HTR

The loss of MAM (previously 901.016) is caused by various inactivating mutations in *EMP3*. A total of eleven MAM negative probands have been described, including one in New Zealand (143). Anti-MAM causes severe and fatal HDFN, and in vitro tests suggest that anti-MAM is capable of causing HTR (141,144).

042 - EMM

The EMM blood group system is encoded by Phosphatidylinositol Glycan Anchor Biosynthesis Class G (*PIGG*), on 4p16.3 chromosome (145). The gene encodes an enzyme that has a role in glycosylphosphatidylinositol (GPI) anchor synthesis. Mutations in *PIGG* are associated with intellectual disability, seizures and hypotonia (146).

Table 31. Antigens in the EMM system (147-150)

Name	#	Year Described	Antigen frequency	Clinical significance
Emm	1	2021	>99%	HTR

The loss of Emm (previously 901.008) is caused by inactivating mutations in PIGG. Anti-Emm is thought to be a naturally occurring antibody in Emm negative individuals and has caused one acute HTR (148,149). In vitro tests suggest that a ti-Emm does not cause HDFN, and one recorded pregnancy was unaffected by anti-Emm, but this evidence is not conclusive (150).

043 - ABCC1

The ABCC1 blood group system is encoded by ATP Binding Cassette Subfamily C Member 1 (*ABCC1*), which is found on 16p13.11 chromosome (137). The gene encodes an ATP-binding cassette (ABC) transporter, which plays a role in protection of kidney epithelial cells. The protein is expressed ubiquitously in almost all human tissues (151).

Table 32. Antigens in the ABCC1 system (137)

Name	#	Year Described	Antigen frequency	Clinical significance
WLF	1	2020	>99%	Unknown

The rare null phenotype is caused by an intron deletion (137).

044 - Er

The Er blood group system is encoded by Piezo Type Mechanosensitive Ion Channel Component 1 (*PIEZO1*), which is found on 16q23-q24 chromosome (152). The gene encodes a red cell calcium channel, which helps change RBC volume in response to deformation (153). It is also expressed in the bladder, colon, lung and skin (154).

Table 33. Antigens in the Er system (155)

Name	#	Year Described	Antigen frequency	Clinical significance
Er^a	1	2022	>99%	Unlikely
Er^b	2	2022	<1%	Unknown
Er3	3	2022	>99%	Probable HTR
ERSA	4	2022	>99%	Severe HDFN
ERAMA	5	2022	>99%	Severe HDFN

All antigens in the Er blood group system are the result of a SNP in *PIEZO1*, except for Er3, whose loss is associated with the very rare Er(a-b-) phenotype. Er^a and Er^b are antithetical antigens.

In vitro tests suggest that anti-Er^a is unlikely to be clinically significant, and a small number of incompatible transfusions have been reported without complications. Results of in vitro tests performed to determine the clinical significance of anti-Er3 showed that incompatible RBCs were destroyed faster than normal, suggesting anti-Er3 may be capable of causing HTRs (156).

045 - CD36

The CD36 blood group system is encoded by *CD36*, which is found on 7q11.2 chromosome (156). The gene encodes a type B scavenger receptor with roles in cell signalling, fatty acid transport, and immune cell function (157). It is expressed in a range of immune and non-immune cells in the blood, including the endothelium (158).

Table 34. Antigens in the CD36 system (159)

Name	#	Year Described	Antigen frequency	Clinical significance
CD36.1	1	2023	Unknown	Possible HDFN

DISCUSSION

This report provides an update on what has been learnt about blood group antigens and systems over the last 20 years, and how their antibodies may affect patients in a clinical context. The results of this study had the potential to reveal limitations in our current ability to identify clinically significant antibodies and provide up to date information that will allow requirements of red cells used in red cell antibody screening to be reviewed.

The following blood group antigens produced antibodies that were either clinically significant or likely to be clinically significant: ENEV (MNS45), SARA (MNS47), P^k (P1PK3), CETW (RH63), VONG (KEL28), KEAL (KEL39), KHOZ (KEL41), DISK (DI22), YTGT (YT6), SCAN (SC7), SCAC (SC9), DOMR (DO7), GECT (GE13), INFI (IN3), PX2 (GLOB4), DSLK (RHAG3), Kg (RHAG5), THIN (RHAG7), Jr^a (JR1), Lan (LAN1), Vel (VEL1), At^a (AUG2), ATML (AUG3), ATAM (AUG4), Sd^a (SID1), MAM (MAM1), Emm (EMM1), Er3 (ER3), ERSA (ER4), ERAMA (ER5) and CD36.1.

There were some limitations in the information found during the literature search. Many antigens were only described in one study or abstract, and a few were only referenced by a secondary source. The coverage for each antigen varied; only a handful of studies gave a prediction of clinical significance, in some studies the quantity of antisera was limited, and therefore many studies were unable to estimate antigen or antibody frequency. The identification and classification of antigens is transitioning to molecular sequencing.

Future research could investigate antigen or allele frequencies in different populations as resources permit, as this can help us determine whether their antibodies are likely to appear more frequently. It could also focus on determining the clinical significance of antibodies, using such tests as the monocyte monolayer assay.

CONCLUSION

Blood group systems show a high degree of polymorphism in a large and heterogeneous human population and new variants appear on a continuous basis. Corresponding antibodies can have real-world consequences in transfusion, pregnancy and autoimmunity. This report described 122 blood group antigens and 17 blood group systems that were elucidated in the last 20 years.

AUTHOR INFORMATION

Natalya J Clark, BMLSc, Student[1]
Holly E Perry, PhD, MSc, MPHIL, Lecturer[2]

[1]University of Otago, Dunedin, New Zealand

[2]Department of Pathology, University of Otago, Dunedin, New Zealand

Correspondence: Natalya Clark
email: natalya.clark@protonmail.com

REFERENCES

1. ISBT. Red Cell Immunogenetics and Blood Group Terminology. Amsterdam, the Netherlands: International Society of Blood Transfusion; 2023 [cited 2023 April 1]. Available from: https://www.isbtweb.org/isbt-working-parties/rcibgt.html
2. Reid ME, Lomas-Francis C, Olsson ML. The Blood Group Antigen FactsBook, 3rd ed. Academic Press; 2012; 758.
3. Hodgson JA, Pickrell JK, Pearson LN et al. Natural selection for the Duffy-null allele in the recently admixed people of Madagascar. *Proc R Soc B* 2014; 281(1789): 20140930. Available from: https://doi.org/10.1098/rspb.2014.0930.
4. Karczewski KJ, Francioli LC, Tiao G, Cummings BB et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* 2020; 581: 434-443.
5. Velliquette RW, Palacajornsuk P, Hue-Roye K, et al. Novel GYP(A-B-A) hybrid gene in a DANE+ person who made an antibody to a high-prevalence MNS antigen. *Transfusion* 2008; 45(12): 2618-2623.
6. Velliquette RW, Hu Z, Lomas-Francis C, et al. Novel single-nucleotide change in GYP*A in a person who made an alloantibody to a new high-prevalence MNS antigen called ENEV. *Transfusion* 2010; 50(4): 856-860.
7. Uchikawa M, Tsuneyama H, Ogasawara K, et al. Molecular basis for a novel low frequency antigen in the MNS blood group system. *Vox Sang* 2006; 91(s3): 133.
8. McBean RS, Hyland CA, Hendry JL, et al. SARA: a “new” low-frequency MNS antigen (MNS47) provides further evidence of the extreme diversity of the MNS blood group system. *Transfusion* 2014; 55(6): 1451-1456.
9. Towns D, Hannon J, Hendry J, et al. Hemolytic disease of the fetus and newborn caused by an antibody to a low-prevalence antigen, anti-SARA. *Transfusion* 2011; 51(9): 1977-1979.
10. Lopez GH, Wei L, Ji Y, et al. GYP*Kip, a novel GYP(B-A-B) hybrid allele, encoding the MNS48 (KIPP) antigen. *Transfusion* 2015; 56(2): 539-541.
11. Lopez GH, Wilson B, Liew YW, et al. An alloantibody in a homozygous GYP*Mur individual defines JENU (MNS49), a new high-frequency antigen on glycophorin B. *Transfusion* 2016; 57(3): 716-717.
12. Ito S, Kaito S, Miyazaki T, 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(6): 1287-1293.
13. Hagman JR, Hult AK, Westman JS, et al. Multiple miscarriages in two sisters of Thai origin with the rare Pk phenotype caused by a novel nonsense mutation at the B3GALNT1 locus. *Transfus Med* 2018; 29(3): 202-208.
14. Suchanowska A, Kaczmarek R, Duk M, et al. A single point mutation in the gene encoding Gb3/CD77 synthase causes a rare inherited polyagglutination syndrome. *J Biol Chem* 2012; 287(45): 38220-38230.
15. Westhoff CM, Storry JR, Walker P, et al. A new hybrid RHCE gene (CeNR) is responsible for expression of a novel antigen. *Transfusion* 2004; 44(7); 1047-1051.
16. Lomas-Francis C, Alcantara D, Westhoff C, et al. JAL (RH48) blood group antigen: serologic observations. *Transfusion* 2009; 49(4): 719-724.
17. Hipsky CH, Lomas-Francis C, Fuchisawa A, et al. RHCE*ceCF encodes partial c and partial e but not CELO, an antigen antithetical to Crawford. *Transfusion* 2011; 51(1): 25-31.
18. Westhoff CM, Vege S, Hipsky CH, et al. RHCE*ceAG (254C>G, Ala85Gly) is prevalent in blacks, encodes a partial ce-phenotype, and is associated with discordant RHD zygosity. *Transfusion* 2015; 55(11): 2624-2632.
19. Scharberg EA, Rink G, Roth S, et al. The RHCE*Ce(501A) allele encodes the PARG antigen (RH60). *Transfusion* 2017; 57(2): 484-486.
20. Westhoff CM, Vege S, Horn T, et al. RHCE*ceMO is frequently in cis to RHD*DAU0 and encodes a hrS–, hrB–, RH:–61 phenotype in black persons: clinical significance. *Transfusion* 2013; 53(11): 2983-2989.
21. Poole J, Grimsley S, Thornton N: A novel mutation in RHCE giving rise to the Rh:-51 phenotype and an antibody to a high frequency Rh antigen present on other Rh:-51 cells. Transfus Med. 2012;22(s1):56. Cited in: Storry JR, Clausen FB, Castilho L, 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* 2018; 114(1): 95-102.
22. Flower R, Wilson B, Davidson C, et al. A case of HDFN defines a novel low frequency Rh antigen associated with indigenous heritage and identified in a blood group genomic study. *Intern Med J* 2021; 51(s6): 6-9.
23. Crew VK, Thornton N, Burton N, et al. Two heterozygous mutations in an individual result in the loss of a novel high incidence Lutheran antigen Lurc. *Transfus Med* 2009; 19(1): 1-19.
24. Hustinx H, Lejon-Crottet S, Henny C, et al. LUIT: a novel high incidence antigen in the Lutheran blood group system. *Vox Sang* 2014; 107(s1): 172.
25. Floch A, Lomas-Francis C, Vege S, et al. A novel high-prevalence antigen in the Lutheran system, LUGA (LU24), and an updated, full-length 3D BCAM model. *Transfusion* 2023; 63(4): 798-807.
26. Crew VK, Laundy R, Bahashwan A, et al. Two novel high incidence antigens in the Lutheran blood group system (LUAC and LUBI). *Vox Sang*. 2016; 111(s1): 63.
27. Vrignaud C, Ramelet S, Amiranoff D, et al. Characterization of a Novel High-Prevalence Antigen in the Lutheran Blood Group System. *Transfusion*. 2018; 58(s2): 6A-254A.
28. Crew VK, Mayer B, Baglow L, et al. A novel high frequency antigen in the Lutheran blood group system (LUNU). *Vox Sang*. 2019; 114(s1): 5-240.
29. Yosephi L, Crew VK, Shinar E, 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(s1): 5-240.
30. Alsubhi S, Mankelow T, Crew VK et al. The expression of BCAM c.674G>A in K562 and HEK293T cell lines helps to define a novel Lutheran antigen LUOM. *Vox Sang* 2023; 118(S1): 6-118.
31. Grey D, Poole J, Martin P, et al: Haemolytic disease of the newborn caused by a new Kell antigen. *Transfus Med*. 2003; 13(1): 30. Cited in: Daniels GL, Fletcher A, Garratty G, et al. Blood group terminology 2004: from the International Society of Blood Transfusion committee on terminology for red cell surface antigens. *Vox Sang*. 2004; 87(4): 304-316.
32. Lee S, Debnath AK, Wu X, et al. Molecular basis of two novel high-prevalence antigens in the Kell blood group system, KALT and KTIM. *Transfusion*. 2006; 46(8): 1323-1327.
33. Boturão-Neto E, Bordin JO. Frequencies of KEL*29 (KALT) and KEL*30 (KTIM) alleles in blood donors and patients with hemoglobinopathies in Brazil. *Transfusion* 2007; 47(8): 1552.
34. Uchikawa M, Onodera T, Ogasawara K, Tsuneyama H, Toyoda C, Yabe R, Enomoto T, Satake M, Nakajima K. Molecular basis for a novel low-frequency antigen in the Kell blood group system, KYO. *Vox Sang* 2006; 91(s3): 136.
35. Velliquette RW, Hue-Roye K, Lomas-Francis C, et al. Molecular basis of two novel and related high-prevalence antigens in the Kell blood group system, KUCI and KANT, and their serologic and spatial association with K11 and KETI. *Transfusion* 2013; 53(11pt2): 2872-2881.
36. Crew VK, Poole J, Watson T, et al. KASH (KEL34): A novel high incidence antigen in the Kell blood group system. *Vox Sang* 2010; 99(s1): 357.

37. Crew VK, Poole J, Bullock T, et al. KELP (KEL35): A New High Incidence Antigen in the Kell Blood Group System Defined By Two Homozygous Missense Mutations in KEL. *Transfus Med* 2010; 20(s1): 30.
38. Crew VK, Poole J, Bullock T, et al. KETI, a novel high incidence antigen in the Kell blood group system: a serological and molecular study. *Vox Sang* 2011; 101(s1): 19.
39. Lomas-Francis C, Vege S, Velliquette RW, et al. Expansion of the Kell blood group system: two new high-prevalence antigens and two novel K0 (Kellnull) phenotypes. *Transfusion* 2013; 53(11pt2): 2887-2891.
40. Lomas-Francis C, Fuchisawa A, Uchikawa M, et al. A new high prevalence Kell antigen KYOR, antithetical to the low-prevalence antigen KYO, is the second trypsin-sensitive Kell antigen. *Transfusion* 2012; 53(s3):158A-159A.
41. Scharberg EA, Wieckhusen C, Luz B, et al. Fatal hemolytic disease of the newborn caused by an antibody to KEAL, a new low-prevalence Kell blood group antigen. *Transfusion* 2016; 57(1): 217-8.
42. Martin-Blanc S, Laget L, Babinet J, et al. Characterization of a novel high-prevalence antigen in the KEL blood group system. *Vox Sang* 2022; 117(s1): 56.
43. Hyland C, Buhariwala K, Lopez G et al. Intertwining roles for genomics and international data sharing defines a novel low prevalence Kell antigen in a blood donor. *Transfusion Medicine* 2022; 32(s3): 3-37.
44. Poole J, Thornton NM, Tilley L, et al. Novel high incidence antigen in the Diego blood group system (DISK) and the clinical significance of anti-DISK. *Vox Sang* 2010; 99(s1): 54-55.
45. Scharberg EA, Stürtzel A, Rothenberger-Mürb S, et al. A new low prevalence Diego blood group antigen found in a Caucasian blood donor. *Vox Sang* 2021; 116(s1): 29.
46. Laundy R, Crew VK, Davies H, et al. A novel high frequency antigen in the Yt blood group system. *Transfus Med* 2017; 27(s2): 42-43.
47. Crew VK, Laundy R, Walser P, et al. Serological and molecular characterisation of a novel high frequency antigen in the Yt blood group system. *Vox Sang* 2018; 113(s1): 63.
48. Van Buren NL, Gillen B, Lomas-Francis C, et al. YTGT: A new high-prevalence antigen in the Yt blood group system in two unrelated Native Americans and transfusion management. *Transfusion* 2022; 62(9): 1917-1922.
49. Hue-Roye K, Chaudhuri A, Velliquette RW, et al. STAR: a novel high-prevalence antigen in the Scianna blood group system. *Transfusion* 2005; 45(2): 245-247.
50. Flegel WA, Chen Q, Reid ME, et al. SCER and SCAN: two novel high-prevalence antigens in the Scianna blood group system. *Transfusion* 2005; 45(12): 1940-1944.
51. Srivastava K, Albasri J, Alsuhaibani OM, et al. SCAR: The high-prevalence antigen 013.008 in the Scianna blood group system. *Transfusion* 2020; 61(1): 246-254.
52. Floch A, Lomas-Francis C, Vege S, et al. Two new Scianna variants causing loss of high prevalence antigens: ERMAP model and 3D analysis of the antigens. *Transfusion* 2022; 63(1): 230-238.
53. Mayer B, Thornton N, Yürek S, et al. New antigen in the Dombrock blood group system, DOYA, ablates expression of Doa and weakens expression of Hy, Joa, and Gya antigens. *Transfusion* 2010; 50(6): 1295-1302.
54. Costa FPS, Hue-Roye K, Sausais L, et al. Absence of DOMR, a new antigen in the Dombrock blood group system that weakens expression of Dob, Gya, Hy, Joa, and DOYA antigens. *Transfusion* 2010; 50(9): 2026-2031.
55. Crew VK, Poole J, Marais I, et al. DOLG, a novel high incidence antigen in the Dombrock blood group system. *Vox Sang* 2011; 101(s1): 263.
56. Crew VK, Thornton N, Bullock T, et al. Serological and molecular characterisation of DOLC, a novel high incidence antigen in the Dombrock blood group system. *Vox Sang* 2013; 105(s1): 30.
57. Shakarian G, Vege S, Hue-Roye K, et al. A Dombrock System Antibody Detects a New High-Prevalence Antigen, DODE. *Transfusion* 2015; 55(s3): 35A-36A.
58. Arnaud L, Helias V, Menanteau C, et al. A functional AQP1 allele producing a Co(a–b–) phenotype revises and extends the Colton blood group system. *Transfusion* 2010; 50(10): 2106-2116.
59. Lopez GH, Wilson B, Millard GM, et al. A new high-prevalence LW antigen detected by an antibody in an Indigenous Australian homozygous for LW*A c.309C>A variant. *Vox Sang* 2022; 117(7): 958-965.
60. Yabe R, Uchikawa M, Tuneyama H, et al. Is: a new Gerbich blood group antigen located on the GPC and GPD. *Vox Sang* 2008; 87(s3): 79.
61. Poole J, Tilley L, Hudler P, et al. Novel mutations in GYPC giving rise to lack of Ge epitopes and anti-Ge production. *Vox Sang* 2008; 95(s1): 181.
62. Lomas-Francis C, Tahiri T, Vege S, 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(s5): 13A.
63. Shakarian G, Ong J, Vege S, et al. A New Antibody in the Gerbich Blood System against a Novel High Prevalence Antigen Named GEAR. *Transfusion* 2016; 56(s4): 140A
64. Banks J, Poole J, Ahrens N, et al. SERF: a new antigen in the Cromer blood group system. *Transfus Med* 2004; 14(4): 313-318.
65. Suwanwootichai P, Phiancharoen S, Bejrachandra S, et al. Cromer system: SERF negative Thai patient with allo anti-SERF. *Vox Sang* 2022; 117(s1): 191.
66. Hue-Roye K, Lomas-Francis C, Belaygorod L, et al. Three new high-prevalence antigens in the Cromer blood group system. *Transfusion* 2007; 47(9): 1621-1629.
67. Crew VK, Poole J, Thornton N, et al. Two unusual cases within the Cromer blood group system: I) a novel hgh incidence antigen Croz and II) a novel molecular basis of Inab phenotype. *Transfus Med* 2010; 20(s1): 12.
68. Crew VK, Poole J, Mathlouthi R, et al. A novel Cromer blood group system antigen, CRUE, arising from two heterozygous DAF mutations in one individual with the corresponding anti-CRUE. *Vox Sang* 2012; 103(s1): 56.
69. Lomas-Francis C, Fuchisawa A, Hamilton J, et al. CRAG: A new high-prevalence antigen in the Cromer blood group system. *Vox Sang* 2012; 103(s1): 211.
70. Asher O, Finkel L, Yosephi L, et al. CROK (CROM19): A new high-prevalence antigen in the Cromer blood group system. *Transfusion* 2021; 61(11): E85-E87.
71. Vrignaud C, Chiaroni J, Durieux-Roussel E, et al. CORS (CROM20): A new high-prevalence antigen in the Cromer blood group system. *Transfusion* 2020; 60(11): E40-E42.
72. Moulds JM, Pierce S, Peck KB, et al: KAM: a new allele in the Knops blood group system. Transfusion 2005; 45:27A. Cited in: Daniels G, Flegel WA, Fletcher A, et al. International Society of Blood Transfusion Committee on Terminology for Red Cell Surface Antigens: Cape Town report. *Vox Sang* 2007; 92(3): 250-253.
73. Scharberg EA, Rink G, Schulz D, et al. KDAS, a new blood group antigen in the Knops blood group system antithetical to KCAM. *Transfusion* 2020; 60(8): E25-E27.
74. Grueger D, Zeretzke A, Habicht CP, 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(10): 2408-2418.
75. Bugert P. Knops blood group system: A molecular view. *Vox Sang* 2023; 118(s1): 6-118.
76. Weinig E, Rink G, Stürtzel A, et al. KNMB, a novel Knops blood group antigen located in LHR-C. *Transfusion* 2023. Available from: https://doi.org/10.1111/trf.1754.
77. Poole J, Tilley L, Warke N, et al. Two missense mutations

in the CD44 gene encode two new antigens of the Indian blood group system. *Transfusion* 2007; 47(7): 1306-1311.
78. Jones B, Joshi S, Crew VK, et al. A new high incidence antigen of the Indian blood group system. *Transfus Med* 2016; 26(s2): 20-21.
79. Henny C, Thornton N, Crottet SL, et al. An antibody against a novel high incidence antigen in the Indian blood group system. *Vox Sang* 2018; 113(s1): 231.
80. Crew VK, Daniels G, Poole J. A New Variant in the OK Blood Group System. *Transfus Med* 2003; 13(s1): 32.
81. Crew VK, Thomas R, Gillen B, et al. A Novel Variant in the Ok Blood Group System. *Transfus Med* 2006; 16(s1): 41.
82. Seltsam A, Strigens S, Levene C, et al. The molecular diversity of Sema7A, the semaphorin that carries the JMH blood group antigens. *Transfusion* 2006; 41(1): 133-146.
83. Richard M, St-Laurent J, Perreault J, et al. A new SEMA7A variant found in Native Americans with alloantibody. *Vox Sang* 2010; 100(3): 322-326.
84. Tilley L, Laundy R, van der Mark-Zoet J, Folman C, de Haas M, Thornton N, Daniels G. Homozygosity for a Variant SEMA7A Allele Resulting in Loss of a Novel High Frequency JMH Antigen. *Transfus Med* 2014; 24(s2): 27-28.
85. Vrignaud C, Ramelet S, Herb A, et al. Characterization of a novel high-prevalence antigen in the JMH blood group system. *Vox Sang* 2019; 114(s1): 52-3.
86. Henny C, Thornton N, Laundy R, et al. An antibody against a novel high prevalence antigen in the JMH blood group system. Vox Sang . 2020; 115(s1): 231.
87. Westman JS, Benktander J, Storry JR, et al. Identification of the Molecular and Genetic Basis of PX2, a Glycosphingolipid Blood Group Antigen Lacking on Globoside-deficient Erythrocytes. *J Biol Chem* 2015; 290(30): 18505-18518.
88. Hagman JR, Barone A, Westman J, et al. β1,3GalNAc-T1-dependent extension of the human blood group B antigen results in a novel ABO-related glycolipid structure on erythrocytes. *Vox Sang* 2019; 114(s1): 53.
89. Tilley L, Green C, Poole J, et al. A new blood group system, RHAG: three antigens resulting from amino acid substitutions in the Rh-associated glycoprotein. *Vox Sang* 2010; 98(2): 151-159.
90. Tanaka M, Abe T, Minamitani T, et al. The Kg-antigen, RhAG with a Lys164Gln mutation, gives rise to haemolytic disease of the newborn. *Br J Haematol* 2020; 191(5): 920-926.
91. 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(2): 98-100.
92. Kubo S, Takahashi J, Yoshizawa H, et al. Male newborn with anti-Kg antibody-induced hemolytic disease of the newborn. *Pediatr Int* 2009; 51(4): 582-584.
93. Tanaka M, Horikawa T, Kusumi T, et al. Anti-Kg antibodies induce monocyte phagocytosis of the red blood cells. *Transfusion* 2021; 61(10): 3050-3051.
94. Gonzalez-Santesteban C, Nogués N, Ruiz NB, et al. Identification of a new low prevalence antigen in the RHAG glycoprotein. *Vox Sang* 2022; 117(s1): 55-56.
95. Long S, Millard G, Liew YW. Haemolytic disease of the fetus and newborn caused by a novel RhAG antigen with c.140T>C (p.Phe47Ser) missense mutation. *Transfus Med* 2022; 32(s3): 3-37.
96. Svensson L, Hult AK, Stamps R, et al. Forssman expression on human erythrocytes: biochemical and genetic evidence of a new histo-blood group system. *Blood* 2013; 121(8): 1459-1468
97. Wieckhusen C, Rink G, Scharberg EA, et al. A new genetic background for the Jr(a–) blood group phenotype caused by the ABCG2*439T allele encoding a p.Arg147Trp change. *Transfusion* 2017; 57(12): 3063-3064.
98. Saison C, Helias V, Ballif BA, et al. Null alleles of ABCG2 encoding the breast cancer resistance protein define the new blood group system Junior. *Nat Genet* 2012; 44(2): 174-177.
99. Haer-Wigman L, Soussan AA, Ligthart P, et al. Molecular analysis of immunized Jr(a–) or Lan– patients and validation of a high-throughput genotyping assay to screen blood donors for Jr(a–) and Lan– phenotypes. *Transfusion* 2014; 54(7): 1836-1846.
100. Hundric Haspl HHZ, Jurakovic Loncar JLN, Tomicic TM, et al. The clinical significance of anti-Jr(a): mild or severe? *Vox Sang* 2007; 93(s1): 208-209.
101. Peyrard T, Pham BN, Arnaud L, et al. Fatal hemolytic disease of the fetus and newborn associated with anti-Jra. *Transfusion* 2008; 48(9): 1906-1911.
102. Kwon MY, Su L, Arndt PA, et al. Clinical significance of anti-Jra: report of two cases and review of the literature. *Transfusion* 2004; 44(2): 197-201
103. Helias V, Saison C, Ballif BA, et al. ABCB6 is dispensable for erythropoiesis and specifies the new blood group system Langereis. *Nat Genet* 2012; 44: 170-173.
104. Boswell-Casteel R, Fukuda Y, Schuetz JD. ABCB6, an ABC transporter impacting drug response and disease. *AAPS*; 20(1): 8.
105. Tanaka M, Yamamuro Y, Takahashi J, et al. Novel alleles of Lan− in Japanese populations. *Transfusion* 2014; 54(5): 1438-1439.
106. Cvejic A, Haer-Wigman L, Stephens JC, et al. SMIM1 underlies the Vel blood group and influences red blood cell traits. *Nat Genet* 2013; 45: 542-545.
107. SMIM1 small integral membrane protein 1 (Vel blood group) Homo sapiens (human). United States: National Library of Medicine, 2023. Available from: https://www.ncbi.nlm.nih.gov/gene/388588.
108. Cvejic A, Haer-Wigman L, Stephens JC, et al. SMIM1 underlies the Vel blood group and influences red blood cell traits. *Nat Genet* 2013; 45: 542-545.
109. Becton DL, Kinney TR. An infant girl with severe autoimmune hemolytic anemia: apparent anti-Vel specificity. *Vox Sang* 1986; 51(2): 108-111.
110. Herron R, Hyde RD, Hillier SJ. The second example of an anti-Vel auto-antibody. *Vox Sang* 1979; 36(3): 179-181.
111. Ferrer Z, Cornwall S, Berger R, et al. A third example of haemolytic auto-anti-Vel. *Rev fr transfus immuno hématol* 1984; 27(5): 639-644.
112. Levine P, White JA, Stroup M. Seven Vea (Vel) Negative members in three generations of a family. *Transfusion* 1961; 1(2): 111-115.
113. Van Gammeren AJ, Overbeeke MAM, Idema RN, et al. Haemolytic disease of the newborn because of rare anti-Vel. *Transfus Med* 2008; 18(3): 197-198.
114. Li XF, Lin FQ, Li JP. Identification of c.238 A>G (p.Arg80Gly) of CD59 blood group gene. *Transfusion* 2018; 58(12): 3033-3034.
115. Madjd Z, Pinder SE, Paish C, et al. Loss of CD59 expression in breast tumours correlates with poor survival. *J Pathol* 2003; 200(5): 633-639.
116. Cocuzzi E, Szczotka LB, Brodbeck WG, et al. Tears contain the complement regulator CD59 as well as decay-accelerating factor (DAF). *Clin Exp Immunol* 2001; 123(2): 188-195.
117. Anliker M, von Zabern I, Höchsmann B, et al. A new blood group antigen is defined by anti-CD59, detected in a CD59-deficient patient. *Transfusion* 2014; 54(7): 1817-1822.
118. Mikdar M, González-Menéndez P, Cai X, et al. The equilibrative nucleoside transporter ENT1 is critical for nucleotide homeostasis and optimal erythropoiesis. *Blood* 2021; 137(25): 3548-3562.
119. Daniels G, Ballif BA, Helias V, et al. Lack of the nucleoside transporter ENT1 results in the Augustine-null blood type and ectopic mineralization. *Blood* 2015; 125(23): 3651-3654.
120. Sweener JD, Holme S, McCall LA, et al. At(a−) phenotype: description of a family and reduced survival of At(a+) red

cells in a proposita with anti-Ata. *Transfusion* 1995; 35(1): 63-67.
121. Cash KL, Brown T, Sausais L, et al. Severe delayed hemolytic transfusion reaction secondary to anti-Ata. *Transfusion* 2002; 39(8): 834-837.
122. Culver PL, Brubaker DB, Sheldon RE, et al. Anti-Ata causing mild hemolytic disease of the newborn. *Transfusion* 1987; 27(6): 468-470.
123. Millard GM, McGowan EC, Wilson B, et al. A proposed new low-frequency antigen in the Augustine blood group system associated with a severe case of hemolytic disease of the fetus and newborn. *Transfusion* 2018; 58(5): 1320-1322.
124. Vrignaud C, Mikdar M, Duval R, et al. Molecular and structural characterization of a novel high-prevalence antigen of the Augustine blood group system. *Transfusion* 2023; 63(3): 610-618.
125. Omae Y, Ito S, Takeuchi M, et al. Integrative genome analysis identified the KANNO blood group antigen as prion protein. *Transfusion* 2019; 59(7): 2429-2435.
126. PRNP gene. Bethesda, United States: National Library of Medicine, 2014. Available from: https://medlineplus.gov/genetics/gene/prnp/
127. Ogasawara K, Omae Y, Ito S, et al. The new blood group system no, 37 - "Kanno". *Vox Sang* 2020; 115(s1): 59.
128. Bullock T, Folman C, van der Mark-Zoet J, et al. The first example of anti-KANNO found outside of Japan. *Vox Sang* 2015; 109(s1): 261.
129. Gassner C, Castilho L, Chen Q, et al. 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. *Vox Sang* 2022; 117(1): 1332-1344.
130. Stenfelt L,Hellberg Å, Möller M, et al. Missense mutations in B4GALNT2 in Sd(a–) individuals with anti-Sda enable genotypic prediction of Sda deficiency and form the basis of a new blood group system. *Transfus Med* 2019; 29(s2): 21.
131. Veldhuisen B, Ligthart P, van der Mark-Zoet J, 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(s1): 193.
132. Reznicek MJ, Cordle DG, Strauss RG. A hemolytic reaction implicating Sda antibody missed by immediate spin crossmatch. *Vox Sang* 1992; 62(3): 173-175.
133. Peetermans ME, Cole-Dergent J. Haemolytic transfusion reaction due to Anti-Sda. *Vox Sang* 1970; 18(1): 67-70.
134. Santoso S. New insights into TRALI: activation of monocytes and endothelial cells as triggers of transfusion-related acute lung injury. *Vox Sang* 2012; 103(s1): 20.
135. Flesch BK, Wesche J, Berthold T, et al. Expression of the CTL2 transcript variants in human peripheral blood cells and human tissues. *Transfusion* 2013; 53(12): 3217-3223.
136. Vrignaud C, Mikdar M, Koehl B, 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(s3): 18A.
137. Sugier H, Vrignaud C, Duval R et al. Null allele of ABCC1 encoding the multidrug resistance protein 1 defines a novel human blood group system. *Vox Sang.* 2020; 115(S1): 40-41.
138. Sassi Y, Lipskaia L, Vandecasteele G, et al. Multidrug resistance-associated protein 4 regulates cAMP-dependent signaling pathways and controls human and rat SMC proliferation. *J Clin Invest* 2008; 118(8): 747-757.
139. Reid G, Wielinga P, Zelcer N, et al. The human multidrug resistance protein MRP4 functions as a prostaglandin efflux transporter and is inhibited by nonsteroidal antiinflammatory drugs. *Proc Natl Acad Sci USA* 2003; 100(16): 9244-9249.
140. Azouzi S, Mikdar M, Hermand P, et al. Lack of the multidrug transporter MRP4/ABCC4 defines the PEL-negative blood group and impairs platelet aggregation. *Blood* 2020; 135(6): 441-448.
141. Baglow L, Tilley L, Crew VK, et al. A novel EMP3 null allele detected in a patient with the MAM- phenotype. *Vox Sang* 2021; 116(s1): 32-33.
142. Zhang N, Zhu HP, Huang W, et al. Unraveling the structures, functions and mechanisms of epithelial membrane protein family in human cancers. *Exp Hematol Oncol 2022* Oct 10;11:69.
143. Thornton N, Crew VK, Tilley L, et al. Disruption of the tumour-associated EMP3 enhances erythroid proliferation and causes the MAM-negative phenotype. *Nature Communication*s 2020; 11: 3569.
144. Montgomery Jr WM, Nance SJ, Donnelly SF, et al. MAM: a "new" high-incidence antigen found on multiple cell lines. *Transfusion* 2002; 40(9): 1132-1139.
145. PIGG phosphatidylinositol glycan anchor biosynthesis class G. United States, National Library of Medicine. 2023. Available from: https://www.ncbi.nlm.nih.gov/gtr/genes/54872/
146. Makrythanasis P, Kato M, Zaki MS, et al. Pathogenic Variants in PIGG Cause Intellectual Disability with Seizures and Hypotonia. *Am J Hum Genet* 2016; 98(4): 615-626.
147. McOmish C. A monthly roundup of key articles in other journals. *Transfusion* 2021; 62(1): 11-13
148. Daniels GL, Taliano V, Klein MT, McCreary J. Emm, a red cell antigen of very high frequency. *Transfusion* 1987; 27(4): 319-321.
149. Takahashi J, Date E, Kusumi T, et al. The first example of an acute hemolytic transfusion reaction due to anti-EMM and the first Japanese proband. *Vox Sang* 2013; 105(s2): 21.
150. Wagner MM, van Dunné FM, Kuipers I, et al. Anti-Emm in a pregnant patient - case report. *Vox Sang* 2013; 106(4): 385-386.
151. Jiye Y, Jianting Z. Multidrug resistance-associated protein 1 (MRP1/ABCC1) polymorphism: from discovery to clinical application. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2011; 36(10): 927–938.
152. Andolfo I, Alper SL, De Franceschi L, et al. Multiple clinical forms of dehydrated hereditary stomatocytosis arise from mutations in PIEZO1. *Blood* 2013; 121(19): 3925-3935.
153. Antonelou MH. Tools and metrics for the assessment of post-storage performance of red blood cells: no one is left over. *Transfusion* 2022; 63(1): 1-6
154. Coste B, Mathur J, Schmidt M, et al. Piezo1 and Piezo2 are essential components of distinct mechanically-activated cation channels. *Science* 2010; 330(6000): 55-60.
155. Crew VK, Tilley LA, Satchwell TJ, et al. Missense mutations in PIEZO1, encoding the Piezo1 mechanosensor protein, define the Er red blood cell antigens. Blood. 2022. Cited In: McOmish C. A monthly roundup of key articles in other journals. *Transfusion* 2022; 63(1): 7-10.
156. Rać ME, Safranow K, Poncyljusz W. Molecular Basis of Human CD36 Gene Mutations. *Mol Med* 2007; 13: 288-296.
157. Chen Y, Zhang J, Cui W, Silverstein RL. CD36, a signaling receptor and fatty acid transporter that regulates immune cell metabolism and fate. *J Exp Med* 2022; 219(6): e20211314. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9022290/
158. van Schravendijk MR, Handunnetti SM, Barnwell JW, Howard RJ. Normal Human Erythrocytes Express CD36, an Adhesion Molecule of Monocytes, Platelets, and Endothelial Cells. *Blood* 1992; 80(8): 2105-2114.
159. Alattar AG, Storry JR, Olsson ML. Challenging the definition of a blood group: proposal to make CD36 a novel blood group system based on a case report and pre-existing genetic, proteomic and clinical data. *Vox Sang* 2023; 118(s1): 6-118.